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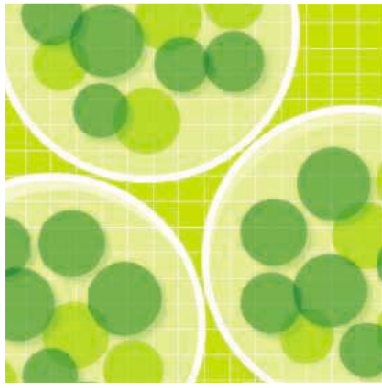

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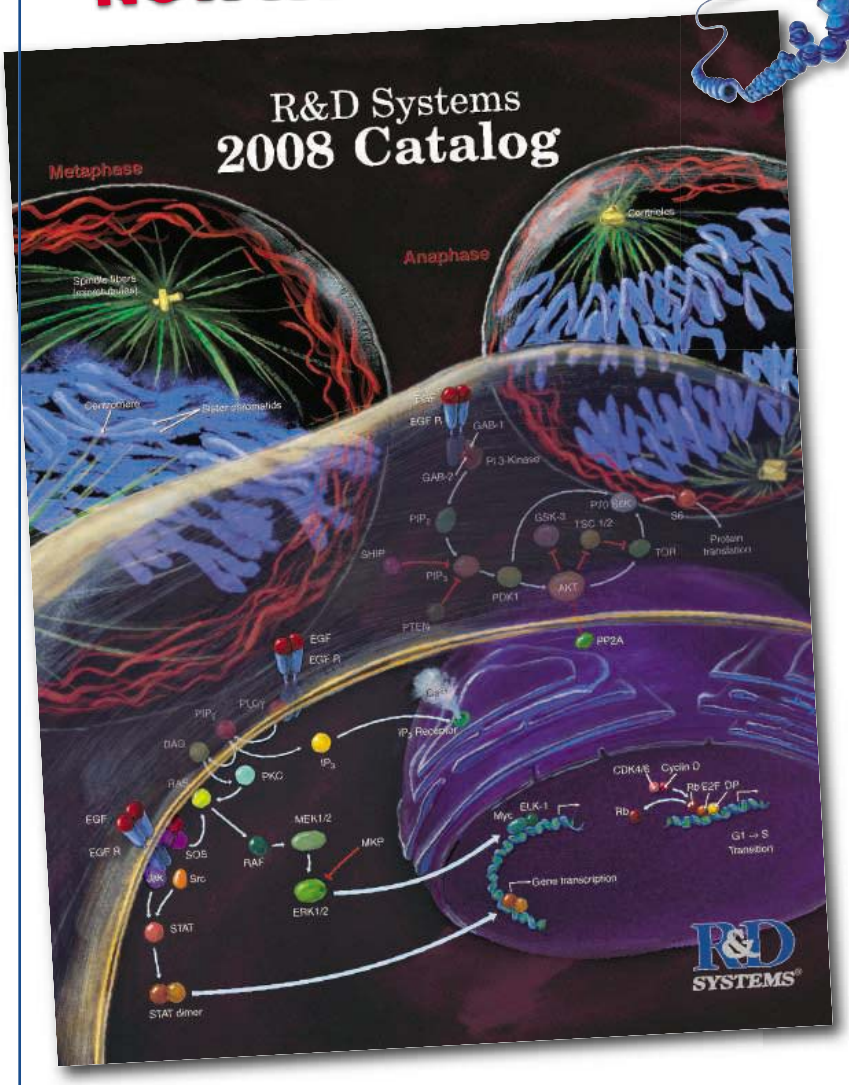

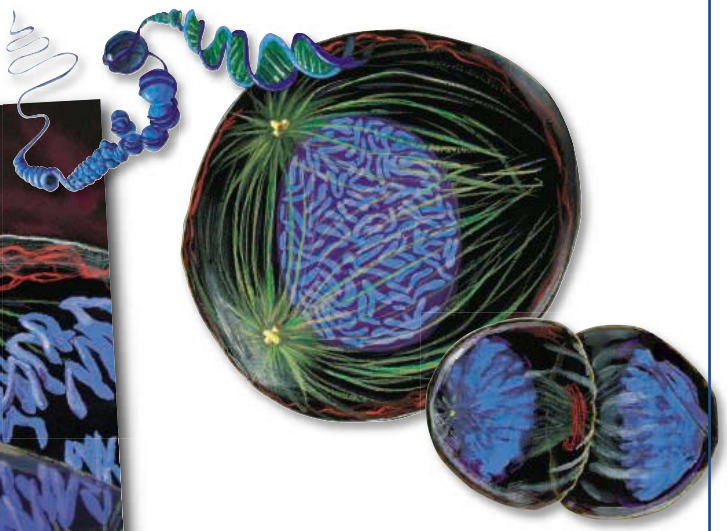

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Volume 319, Issue 5862

COVER

A male lark bunting in the Pawnee National Grassland, Colorado. The plumage quality of the males determines their reproductive success, but different aspects of the black and white markings are preferred by females in different years. This variability alters the long-term sexual selection dynamics and may favor the evolution of multiple sexual ornaments. See page 459.

Photo: Bruce Lyon

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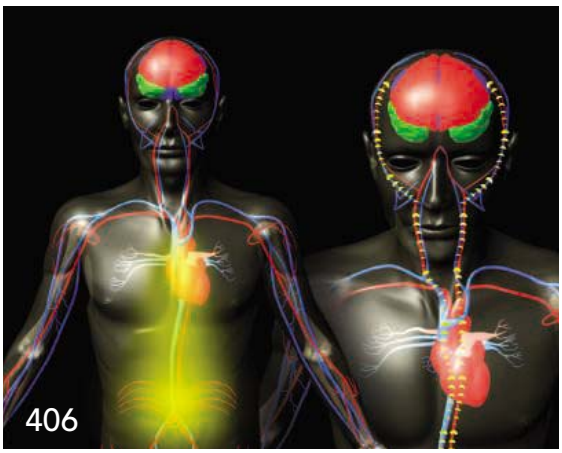
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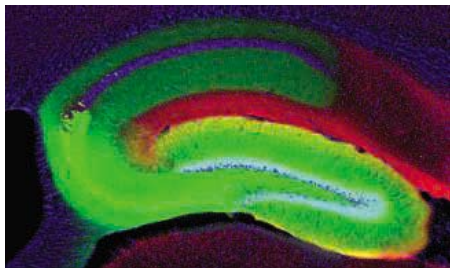

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miRNAs and Cancer Webinar

It is well established that microRNAs play a critical role in developmental and in many physiological processes by regulating target gene expression at the posttranscriptional level. It should therefore not be surprising that deregulation or dysregulation of miRNA expression could result in specific disease phenotypes. Increased interest in the potential function of miRNAs in tumorigenesis has rapidly propelled research forward as new technologies, or the adaptation of old technologies, have allowed researchers to obtain better miRNA expression profiles and more accurately identify target sites.

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Human ITPK1.

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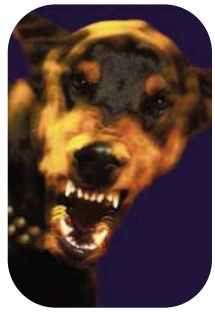
PERSPECTIVE: Human ITPK1—A Reversible Inositol Phosphate Kinase/Phosphatase that Links Receptor-Dependent Phospholipase C to Ca^{2+}-Activated Chloride Channels
A. Saiardi and S. Cockcroft
Studies of ITPK1 reveal subtle interconnections between simple metabolism and regulation of a signaling event.

GLOSSARY
Find out what NOSIP, SIPK, and STAND mean in the world of cell signaling.



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Dissecting Stardust Origins >>

Stardust recently returned the first samples collected from a known comet. It was thought that these samples might resemble interplanetary dust particles (IDPs), which are also thought to come from comets and have been collected in Earth's stratosphere and elsewhere on Earth, such as in polar ice. **Ishii *et al.*** (p. 447; see news story by **Kerr**) directly compare silicate grains from Stardust and IDPs and show that this is not the case. Instead, the Stardust samples resemble grains from meteorites. These findings imply that there is a continuum between asteroids and comets, that at least this comet does not have much material from the outer solar system, and that the IDPs may be the most primitive remaining material in the solar system.

Spinning Odds and Evens

The need for a net change in electronic spin along a reaction pathway usually leads to substantial slowdown of the overall transformation. **Burgert *et al.*** (p. 438) show that this spin-conservation principle extends straightforwardly to a series of small anionic metal clusters comprised of ~10 to 20 aluminum atoms. Previous studies had revealed a puzzling alternation in the reactivity of odd and even-numbered Al_n^- clusters with oxygen. By varying the spin state of both the clusters (through addition of H atoms) and the O_2 (through excitation to the singlet), the authors obtain mass spectrometric data that correlate reactivity with spin-conserving pathways.

Dynamics of a Dangling Bond

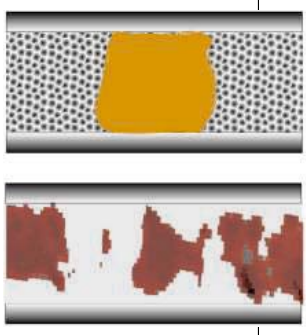
The development and optimization of functional materials and devices depend on thoroughly characterizing the carrier transport properties of the material. As device structures decrease in size, macroscopic characterization techniques may no longer be valid. **Berthe *et al.*** (p. 436, published online 13 December) investigate the transport of inelastic tunneling electrons through a localized state in Si, a dangling bond, and look at how the transport properties are modified by the local microscopic environment.

Core Problem

A major goal of mantle geochemistry has been to find isotopic or chemical signatures of the outer core in mantle-derived materials. Unusual osmium isotope ratios in Hawaiian rocks have been used to argue that such material could rise to the surface from the core through deep mantle plumes. However, this interpretation has been contentious, and other evidence to back it up has been sparse. **Luguet *et al.*** (p. 453; see the Perspective by **Meibom**) demonstrate instead that anomalous Os ratios need not arise from material leaked from the core. Sulfides can affect the fractionation of the Pt-Os and Re-Os systems and result in Os heterogeneities in the mantle itself.

A Look Inside Reactors

Many industrially significant chemical reactions rely on flowing gaseous compounds through packed solid catalysts. Optimization in these heterogeneous environments would benefit from the capacity for detailed mapping of flow patterns and reactive site distributions, but probes of sufficient sensitivity are often lacking. **Bouchard *et al.*** (p. 442) show that magnetic resonance imaging, which typically requires liquid samples, can be applied to the much more diffuse gas-solid interface of a microreactor by signal enhancement from the para nuclear spin isomer of H_2. They probe the hydrogenation of propylene to propane, and find that use of the *p*-H_2 in tandem with precisely timed pulse sequences allows direct visualization of flow velocities and active-catalyst density profiles.



Short-Wavelength Photonics

Reductions in the operational wavelength of laser diodes into the blue and violet has made possible the development of high-density recording media such Blu-ray optical discs. Generally, the laser diodes at the heart of such technology are formed from bulk crystals of GaN. **Matsubara *et al.*** (p. 445, published online 20 December) now show that photonic crystal technology, already demonstrated for surface-emitting lasers at infrared wavelengths, can be scaled down to emit in the blue-violet regime. The possibility to engineer the emission wavelength and polarization mode may enable even higher optical storage densities.

Soft Mantle Signature

Earth's lower mantle extends from depths of 600 to about 2900 kilometers, and for much of this depth the mantle contains two major minerals, perovskite and ferropericlase. Both minerals contain some iron, and at depths below about 1300 kilometers, it has been shown that changes in the spin pairing of the iron affects the properties of these minerals. **Crowhurst *et al.*** (p. 451) measured the stiffness of ferropericlase at high pressures across this transition. With increasing depth across the transition, the mineral becomes progressively softer to the propagation of seismic waves, and more so as the iron content increases. These data

Continued on page 383

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Continued from page 381

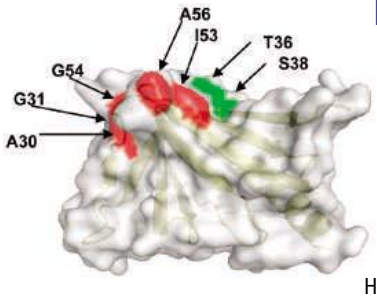
may help explain the lack of a clear seismic signal of a phase transition at depth and may help explain the seismic signatures of the deeper lower mantle.

The Inconstant Female

Female choice is thought to drive evolution through sexual selection. It has been assumed that females over time would show consistent preferences for the same male traits. However, **Chaine and Lyon** (p. 459; cover) found in a long-term study of sexual selection in lark buntings that females have flexible patterns of choice for male traits over several years. This finding explains both the stability of traits under sexual selection and the evolution of multiple male sexual signals. Analyses of phenotypic selection with short time frames can lead to incorrect predictions about the trajectory of sexual selection, which might explain earlier contradictory findings.

Fast and Slow

During gene transcription, some activator proteins bind cyclically to their promoters, with periodicities of ~30 seconds (fast cycling) or ~30 minutes (slow cycling). **Karpova *et al.*** (p. 466) now show that these different cycles are distinct, but that the same transcription activator can engage in both cycling activities on the same promoter at the same time. It seems that the fast cycle is involved in transcription initiation, whereas the slow cycle modulates the number of promoters accessible for initiation.



CREDIT: HUANG *ET AL.*

Homering in on T Cell Activation

In the immune system, T cells are stimulated by signals that emanate from the T cell receptor (TCR) and co-stimulatory cell surface receptors, most notably CD28. CD28 signals profoundly influence the ensuing immune response—TCR stimulation in the absence of CD28 results in anergy, a state of permanent inactivation. **Huang *et al.*** (p. 476) provide evidence that the alternate pathways for a T cell are coordinated by two cytoplasmic scaffolding proteins, Homer2 and Homer3. Absence of these proteins caused unchecked activity of the central cytokine transcriptional regulator NFAT (nuclear factor of activated T cells), up-regulation of cytokine expression, and signs of overt T cell reactivity. Thus, a dynamic decision mechanism dictates whether a T cell will become activated or anergized.

Activating Aurora

Cell division in eukaryotes requires tight spatial and temporal control of its many components. Aurora B kinase, as part of the chromosomal passenger complex (CPC), plays a critical role in regulating chromosome segregation to daughter cells. How is the activity of Aurora B itself controlled? **Rosasco-Nitcher *et al.*** (p. 469) show that Aurora B is regulated at several levels by the protein teleophase disc 60-kD (TD-60), which, like Aurora B, is also found at inner centromeres during metaphase. Interaction with TD-60 brings the CPC to the centromere, and, in combination with microtubules, activates Aurora B. Furthermore, Aurora B can only act on previously phosphorylated substrates, whose phosphorylation is also enhanced by TD-60. Thus, TD-60 may function to ensure that high levels of Aurora B activity occur only at centromeres.

How Yeast Responds to Change

The origin of the rapid adaptive response of yeast cells to changes in environmental osmolarity has been unclear. **Mettetal *et al.*** (p. 482; see the Perspective by **Lipan**) now show that increases in extracellular osmolarity activate the high-osmolarity glycerol signaling pathway, which changes transcription of particular target genes. By measuring the cellular response to pulses of medium with increased ionic strength, the authors were able to develop a predictive model of the dynamics of this regulatory system. Rather than changes in gene expression, which have often been suggested to be at the core of the response to osmotic shock, the fast response is actually dominated by a nontranscriptional response that probably involves altered glycerol transport.

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Michael Greene is a scholar at the National Academies, Washington, DC. E-mail: mgreene@nas.edu.

Solutions for Nigeria

NIGERIA, LIKE MANY MOSTLY RURAL DEVELOPING COUNTRIES, IS NOT ABLE TO PROVIDE all its population with basic services such as safe potable piped water and affordable electric power. The economics of extending the electric grid and water distribution network into the countryside are daunting, and the people who lack electricity, safe water, and effective medicines are usually poor and clustered within extremely dense urban communities or live in highly dispersed rural communities with limited infrastructure. Two-thirds of Nigerians, around 100 million people, lack household electricity, and about as many do not have safe drinking water. Nigeria also has the world's largest burden of people suffering from infectious diseases, mostly malaria, without effective treatment.

Yet there are solutions. In Karnataka, India, the Solar Electric Light Company (SELCO) sells, installs, and services solar home lighting systems to tens of thousands of poor villagers—at a profit. Local subsidiaries of WaterHealth International of California franchise storefront water stores and community purified water systems in developing countries—at a profit. Potters for Peace of Nicaragua supports local companies manufacturing ceramic water filters. These are sustainable solutions in the sense that they do not depend on donor funds or ongoing financial support from a government, because the profit comes from sales to consumers alone. Can the private sector of a country such as Nigeria be mobilized to provide basic services to the population that the government cannot afford—at a profit?

Many companies have developed business models that, incorporated into a new approach to sustainability, can meet the needs of marginal populations for electricity, safe water, and medicines, while providing new sources of jobs and income. Their models include robust, but not necessarily low-tech, products, customer training, microcredit, service contracts, and franchising opportunities. As limiting as the conditions in Nigeria seem to be, the great advantage to a company is the country's huge number of potential clients. In India and other countries with large numbers of poor people, companies aiming at the customer base at the wide bottom of the economic pyramid have produced new, innovative products and services at substantial profit to themselves as well as benefits to their customers. The market in Nigeria for electric power, safe water, and effective malaria therapy exceeds the total populations of all but a handful of countries.

Mobilizing Science-Based Enterprises for Energy, Water, and Medicines in Nigeria, a recent study issued by the U.S. National Academies and the Nigerian Academy of Science, addresses the potential for a sustainable approach to supplying these basic services to Nigeria's poor by encouraging private companies to become involved. This study revolved around the findings of three workshops that joined successful entrepreneurs from other countries, including executives of SELCO, WaterHealth, and Potters for Peace, with Nigerian business leaders and scientists. They prepared business models, including cost estimates, adapted to the Nigerian market for companies to manufacture, sell, and install solar photovoltaic units and water filtration systems for the rural and urban poor, and to produce the ingredients for and manufacture artemisinin combination therapies (ACTs), the most effective treatment for malaria. The malaria venture differs from the other two because of complexities in the malaria drug market. If a global subsidy for ACTs moves forward as expected, Nigerian products would have to meet international quality standards to qualify for the subsidy, and national regulatory quality controls would need to be developed and enforced, without which Nigerian ACTs could not compete with imported products.

The study concludes that businesses providing small-scale photovoltaic systems, low-cost water filtration systems, and malaria drugs (assuming that Nigerian companies qualify for a putative global subsidy for ACTs) could operate profitably in Nigeria and in other countries of the region. But adoption of this approach may require government incentives, educational campaigns, and a corresponding shift in strategy by donor organizations and bilateral aid agencies. International aid programs may have to be reconfigured so that they resemble venture capital companies with a diverse portfolio of investments (taking into account that startup companies may not always succeed) rather than discrete, one-of-a kind grants.

– Rita R. Colwell and Michael Greene

10.1126/science.1155012

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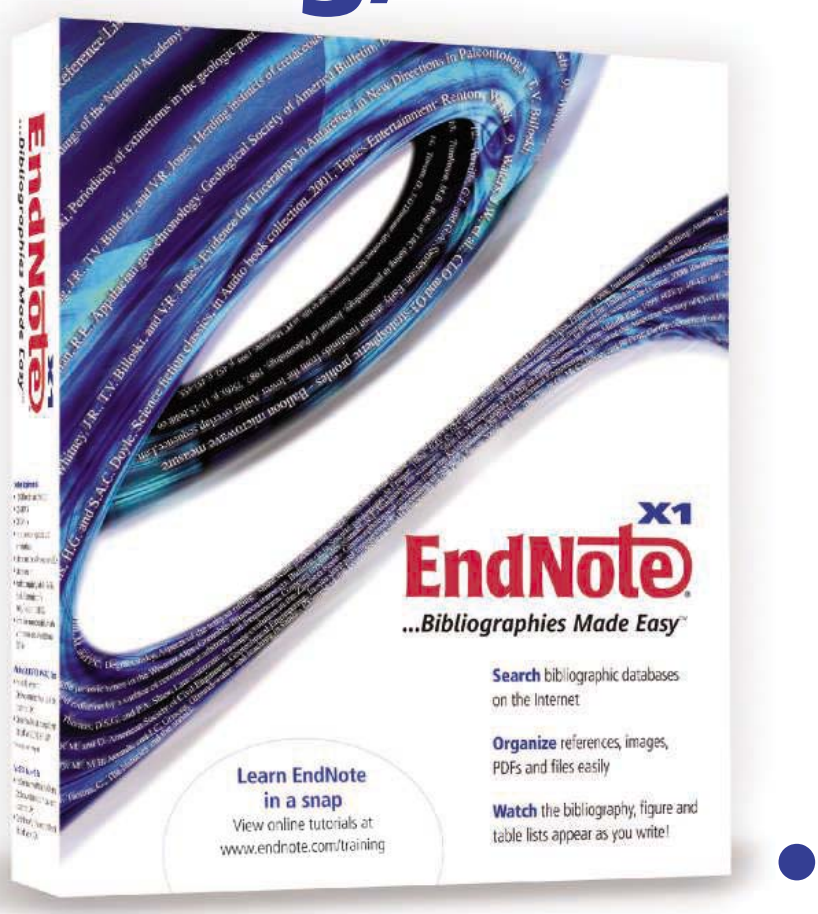

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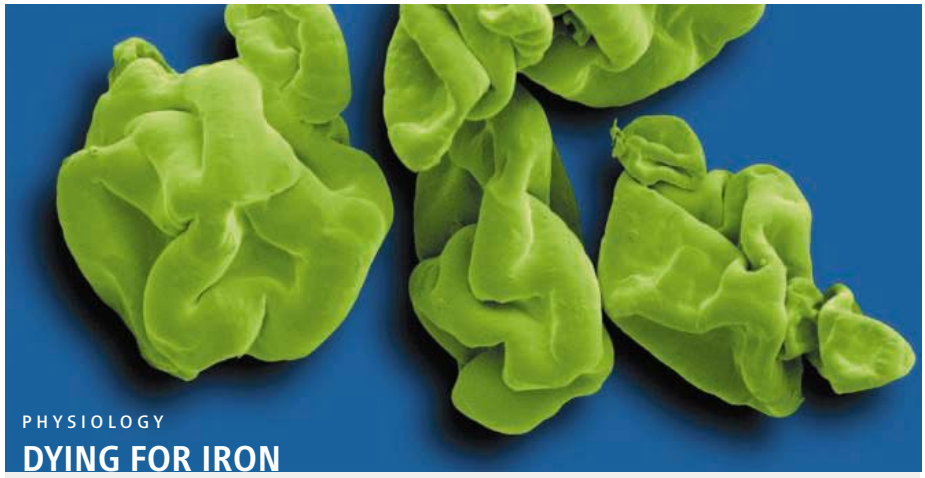
APPLIED PHYSICS

CARS to See Spores

Selective detection of airborne biohazards in a background environment filled with all manner of pollen, dust, and debris remains a serious challenge. Pestov *et al.* have pursued a promising approach based on coherent anti-Stokes Raman scattering (CARS) spectroscopy. In general, Raman-based techniques should offer high specificity based on molecular vibrational signatures, but they have been plagued by high background noise due to nonresonant scattering of the light by the molecules in the beam path. The authors' group previously addressed this shortcoming using a precisely timed series of broadband pump and Stokes excitation pulses followed by a delayed narrowband probe, a modification of the more conventional CARS protocol in which pump and probe pulses are closer in time and duration (see Pestov *et al.*, Reports, 13 April 2007, p. 265). They now show that by shifting wavelengths from the visible to the lower-energy near-infrared regime, they can increase the signal strength by raising photon intensity while avoiding damage to the sample that would preclude identification. Further optimization of the pulse bandwidths and relative timings allowed detection of as few as 10,000 bacterial spores with a single laser shot. — JSY

Proc. Natl. Acad. Sci. U.S.A. **105**, 422 (2008).



PHYSIOLOGY

DYING FOR IRON

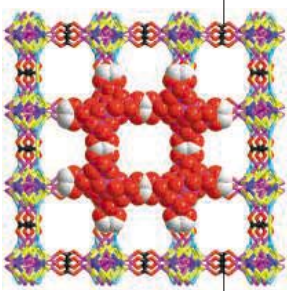
Food supplements, such as the blue-green alga popularly referred to as spirulina, are used worldwide and can serve as valuable sources of vitamins and minerals. Iron is one of the many elements that are needed for life yet are toxic in excess. In the small intestine—particularly in the first 12–finger-width segment known as the duodenum—epithelial cells express the iron-regulatory proteins (IRP1 and IRP2) that maintain iron homeostasis by adjusting the expression of proteins that absorb, metabolize, and export this essential dietary component. By selectively eliminating the expression of IRPs in these cells in mice, Galy *et al.* demonstrate that they are also required for intestinal development. They observed that mice deficient in IRPs suffered from weight loss and dehydration and died a few weeks after birth. Surprisingly, the mice manifested close to normal blood and liver iron content; on the other hand, intestinal villi were malformed, and duodenal epithelia displayed degenerated mitochondria (perhaps a sign of diminished iron-sulfur cluster synthesis) and increased cell death, which probably contributed to impaired water and nutrient absorption. Thus, although the absence of IRPs in the intestinal epithelium does not acutely alter systemic iron levels, it does affect intracellular processes that control intestinal morphogenesis and survival. — LDC

Cell Metab. **7**, 79 (2008).

CHEMISTRY

Bright Yellow Glow

One approach for creating white-light sources is to integrate a yellow phosphor with a blue light–emitting source. Yellow phosphors usually comprise rare earth (Ce or Eu) ions in an inorganic host matrix. Recently, it was shown that large-channel Zn-Ga phosphates could exhibit yellow-to-white luminescence. Yang and Wang now report that an organic-inorganic microporous analog is a highly efficient yellow phosphor with photoluminescent quantum efficiencies that can exceed 40%. These materials contain hexameric Ga clusters, $Ga_6(OH)_4O_{26}$, that are connected in a two-dimensional network through bridging phosphate and oxalic acid groups. This anionic framework is charge-balanced by organic dications. The authors suggest that the intrinsic disordered nature of the lattice creates defect sites at pairs of Ga atoms in the largest pore that act as activator sites for emission. — PDS



J. Am. Chem. Soc. **130**, 10.1021/ja7101423 (2008).

PHYSIOLOGY

Give Me Oxygen (or Not)

Recent memorial tributes celebrating the accomplishments of Sir Edmund Hillary, one of the first two men to scale Mount Everest, are a fascinating reminder of the ability of mammals to tolerate low oxygen levels (hypoxia). The physiological response to hypoxia involves the transmission of signals from cellular oxygen-sensing pathways to metabolic enzymes that consume oxygen, but how this occurs is poorly understood. Aragonés *et al.* have studied mice that are deficient in an oxygen-sensitive enzyme that regulates the stability of a transcription factor (hypoxia-inducible factor–1), which is known to activate genes involved in cellular adaptations to hypoxia. Analysis of skeletal muscle in the mutant mice revealed that the loss of this enzyme, called prolyl hydroxylase–1 (Phd1), lowered oxygen consumption by reprogramming basal metabolism; that is, by inducing a selective decrease in glucose oxidation and a switch to more anaerobic glycolysis. Muscle tissue in the Phd1-deficient mice was protected from the necrosis typically seen under acute oxygen deprivation, an outcome apparently due to reduced formation of harmful reactive oxygen species. These findings not only identify Phd1 as a key molecular player regulating hypoxia tolerance but raise the possibility that pharmacological inhibition of the enzyme could have beneficial effects in diseases characterized by oxidative stress and ischemic damage. — PAK

Nat. Genet. **40**, 10.1038/ng.2007.62 (2008).

CREDITS (TOP TO BOTTOM): MEDISCAN/CORBIS, *J. AM. CHEM. SOC.* **130**, 10.1021/JA7101423 (2008)

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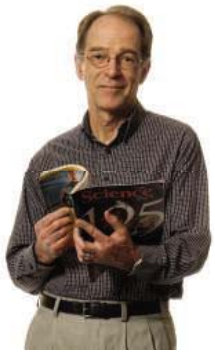

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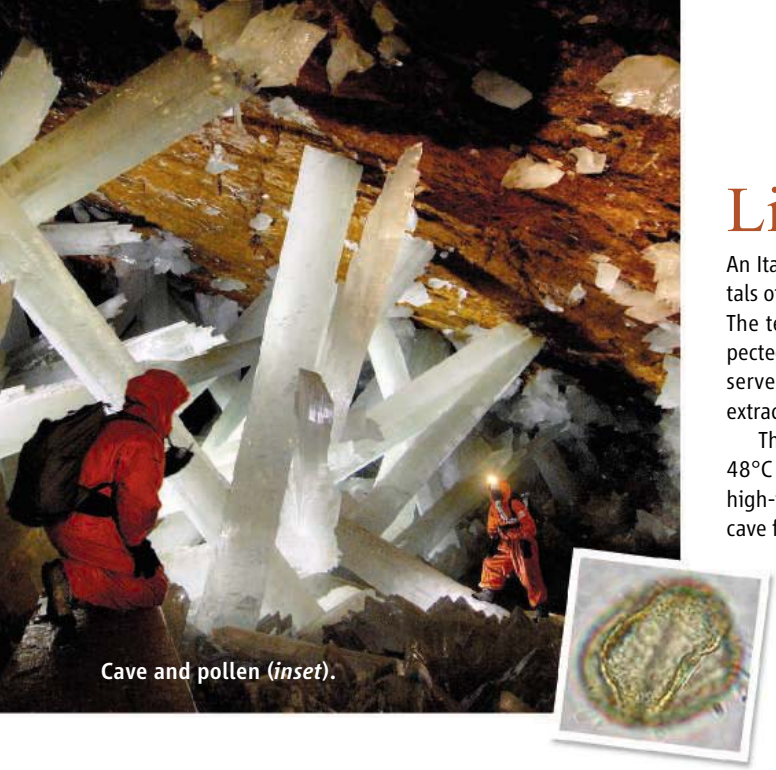


Cave and pollen (*inset*).

Life in Crystal

An Italian research team this winter found ancient pollen sealed in the colossal crystals of the Cueva de los Cristales, a cave in a lead and silver mine in northern Mexico. The team, led by mineralogist Paolo Forti of the University of Bologna, Italy, suspected that the selenite crystals, some as long as 11 meters, could contain pollen preserved when they formed several hundred thousand years ago. Now they have extracted 43 pollen grains in samples from two crystals.

The 290-meter-deep cave was discovered in 2000, but its hellish conditions—48°C and 100% humidity—have limited exploration until recently. Scientists with high-tech suits to cool their bodies and dry the air for breathing can now explore the cave for up to an hour at a time.

The pollen, presumably transported into the cave by underground streams, may help scientists reconstruct ancient climate and vegetation cover in the northern region of the Chihuahua desert, says Forti. Palynologist Anna Maria Mercuri of the University of Modena, Italy, identified the pollen as a type of oak found in the southern United States, which suggests that the area was humid forest. Forti's team is now using radiometric dating to get a definitive age for the crystals.

Body Heat

A Swedish real estate company plans to harness the body heat generated by commuters in Stockholm's main railway station to warm a nearby office building.

"This came up during coffee," says Karl Sundholm, the project leader. "We spent a couple hours doing calculations and found it might be possible." The company, Jernhusen AB, already sucks unneeded heat out of the station through giant ventilators. At a cost of €30,000, the company says it could build a system that uses the hot air to warm water, which would then be pumped through pipes in a building it plans to construct next door. Sundholm estimates that the 250,000 people who pass through the station each day could provide 5% to 15% of the 13-story building's heating needs. "This is not rocket science," says Sundholm. "It is just one good idea."

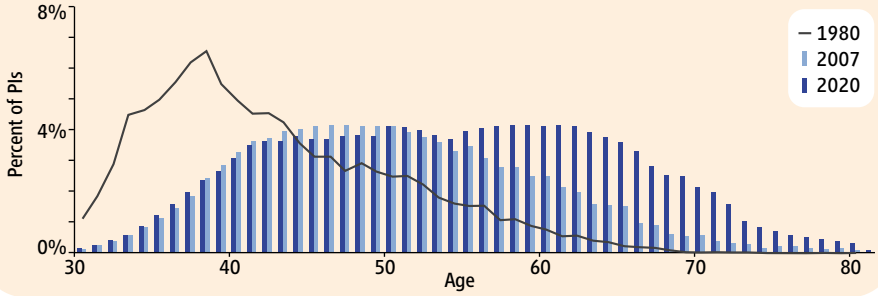
Rufus Ford of Sustainable Energy Action, a London nonprofit, says trying to reuse wasted heat is a good idea regardless of its source. "If it works, the project might be something worth looking into for the London Tube," he says. "It is always warm down there."

THE INCREDIBLE AGING INVESTIGATOR

Science policy experts have been wringing their hands for years about the rising age at which scientists get their first National Institutes of Health (NIH) research grant, now averaging 43. But NIH predicts things are going to get even worse.

Mostly in their 30s and 40s in 1980, principal investigators (PIs) now cluster in a bell curve roughly around age 48. By 2020, the curve will shift and flatten out, with a solid band of scientists spread between 42 and 66 and a tail stretching well into the 70s (see graph). NIH Director Elias Zerhouni, who had demographers and actuaries generate the projections, told his advisory committee last month that he blames the baby boom, rising retirement age, and "cultural factors" such as a peer-review system that favors established PIs.

"We do not have a strategic answer; we have a tactical answer," Zerhouni said, which is to target more awards to young investigators. Committee member Thomas Kelly, director of the Sloan-Kettering Institute in New York City, called the projections "absolutely astounding. … Clearly that's going to have very long term implications for American science."



The Jaywalking Peacock

Men use risk-taking as a sort of mating display, even when trying to catch a bus, says a study in this month's *Evolutionary Psychology*.

During three chilly winter months, a team led by Oxford University psychologist Robin Dunbar watched 524 men and 475 women wait for a 9:40 a.m. bus. Men were more likely to cut it close even though they risked being stranded in the cold by a full bus. The researchers also observed 1000 street-crossings at a Liverpool crosswalk.

The men made more dangerous crossings if women were looking, says Dunbar, which adds to evidence that mating is never far from the male mind. And although men who were alone or with other men left no time to spare at bus stops, men traveling with women conformed to early feminine arrival times. "It shows how a good woman civilizes the boys," concludes Dunbar. Male bystanders had no discernible effect on females' traffic or bus-stop behavior.

Daniel Fessler, an anthropologist at the University of California, Los Angeles, says he likes how the authors, "by studying everyday behaviors in a natural context," show that male risk-taking permeates even pedestrian activities.

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On Campus

ARM'S LENGTH. The pope's presence is supposed to bring peace and harmony. But when the University of Rome "La Sapienza" invited Pope Benedict XVI to mark the institution's 705th academic year last week, faculty members and students kicked up such a fuss that the Vatican called off the visit.

The protests were led by 63 physicists who objected to the pope's views on Galileo. They point to a 1990 speech in which the pope—then Cardinal Ratzinger—quoted philosopher Paul Feyerabend as saying that the church's 17th century persecution of Galileo was "reasonable and just" and that the church had been "far more faithful to reason" than had been the astronomer. Stating that these words "offend and humiliate us," the physicists asked the university's rector, Renato Guarini, to cancel the "incongruous" event. Two days before the inauguration, the Vatican announced that it had decided to cancel the visit "given the events of the last few days."

Italian politicians from both the left and the right have condemned the academics, causing them to clarify their position. "The pope is free to come and visit the university at some other time, but not at the opening of the academic year of the university, which is a secular institution," says Carlo Cosmelli, one of the letter-writers.

DEATHS

OPTIMISM PERSONIFIED. Judah Folkman, whose once-controversial idea that blocking blood-vessel growth can choke tumors is now widely accepted, died last week, apparently of a heart attack, after collapsing at Denver International Airport. He was 74.

Folkman, a fixture at Children's Hospital Boston since the late 1960s and a professor at Harvard Medical School, met with skepticism from many scientists when he first proposed his concept of angiogenesis. But his persistence was legendary. In an interview with *Science* 3 years ago, he emphasized that "if something's really important, you keep after it, regardless of what other people think." His work on angiogenesis opened up a new research field in cancer and other diseases with blood-vessel abnormalities, such as macular degeneration, and led to many new drugs.

Folkman had an unquenchable curiosity and passion for discovery. "He stayed a little kid his entire life," says Donald Ingber, who has worked with Folkman since joining his lab as a postdoctoral fellow in 1984. "The idea that something actually stopped him kind of takes our breath away."

MOVERS

DESERT ROSE. Choon Fong Shih built his academic reputation on understanding how metal cracks under stress. Now the Singapore-born, U.S.-trained materials scientist will be addressing the fault lines in global higher education as the founding president of King Abdullah University of Science and Technology, a new graduate university in Saudi Arabia with a $10 billion endowment.

As vice-chancellor of the National University of Singapore, Shih has transformed a well-regarded undergraduate institute into an Asian research powerhouse. Ali Ibrahim Al-Naimi, the Saudi minister of petroleum and mineral resources and chair of the new university's board of trustees, hopes that Shih will repeat that performance by being "a builder of bridges across peoples, disciplines, institutions, and cultures."

To attract faculty, Shih intends to offer generous, guaranteed funding—"much bigger than the usual start-up package." He also plans to organize the university around multidisciplinary research topics rather than individual departments.

Shih, 62, begins his new job in December, and the university—being built 80 km north of Jeddah—will open its doors in September 2009.

Two Cultures >>

DOCUMENTING DOCUMENTING. Linguists David Harrison and Gregory Anderson of the Living Tongues Institute for Endangered Languages in Salem, Oregon, have trekked to many remote corners of the world to document dying languages. On three recent expeditions, they let a film crew tag along in hopes of furthering efforts to save endangered tongues.

The result is a 70-minute documentary that premiered at the Sundance Film Festival last week. Produced by Ironbound Films and partly funded by the U.S. National Science Foundation, *The Linguists* follows Harrison and Anderson as they travel to Siberia, India, and Bolivia to locate and record the last living speakers of three endangered languages. It captures both the drama and the grunt work involved in the project—from eureka moments with village elders to stomach problems and negotiations with reluctant governments. In one scene, for example, Anderson (left), tutored by native speakers, finally comprehends the "obscenely complex" counting system of the Sora language in the Indian state of Orissa.

Working with a film crew was "a little odd at first," Anderson says, "but eventually, we sort of forgot they were there." Harrison says the filmmakers helped open some doors, arranging a formal presentation to the Bolivian government to make the case for saving the Kallawaya language. "We wouldn't have had that level of access without them," he says. A portion of the proceeds from the film will go toward initiatives to record and revitalize endangered languages.

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CREDITS (TOP TO BOTTOM): EDWIN CARTLIDGE, IRONBOUND FILMS; JON CHASE/HARVARD NEWS OFFICE

Should Max Planck be like Howard Hughes?
396

Catching rays
400

ARCHAEOLOGY

Dust Storm Rising Over Threat to Famed Rock Art in Utah

For more than 1000 years, geometrical human figures, animals, and abstract designs have graced the sandstone walls of Nine Mile Canyon in central Utah. Considered one of the premier rock art sites in North America, the canyon holds at least 10,000 images pecked and painted by the mysterious Fremont and later the Ute Indians.

Now a much-anticipated study just submitted to the U.S. Bureau of Land Management (BLM) warns that truck traffic from nearby oil and gas operations could be fading the splendor of the world-renowned rock art. "The results of my study are very alarming," says report author Constance Silver, an art conservator with Preservar Inc. in Brattleboro, Vermont.

The report, due to be released in a week or two as part of an Environmental Impact Statement (EIS) on expanding oil and gas operations in the canyon, is likely to kick up a furious dust storm of its own. BLM managers say they are not convinced that the current operations are causing serious damage. "Obviously, the dust is having an impact on the visual clarity of the rock art. But whether the dust is having a [lasting] impact is open to question," says archaeologist Julie Howard of BLM in Salt Lake City.

Big 18-wheel rigs have been rumbling through Nine Mile Canyon since 2004, when BLM gave energy companies the go-ahead to drill for natural gas higher up in the plateau. The decision had outraged some archaeologists because the art sits just adjacent to the canyon's main, coarsely graded road.

Silver's report is the first to study the effects of the traffic and the dust it creates. One of the few conservators who specializes in rock art, she was commissioned by BLM officials in Utah last year to assess the impacts. She worked in the canyon last April, recording the amount of particles in the air before and after trucks passed by. She also collected particulate samples in heavily trafficked areas and in sparsely visited side canyons (for control). She completed her report late last year and described her results to *Science* earlier this month.

Ironically, Silver found that the chief danger comes from an effort by the Bill Barrett Corp. and other energy companies that use the road to suppress dust: They have repeatedly applied magnesium chloride to the dirt road. This salt damps dust by pulling moisture out of the air. But Silver says the chemical is "flying all over the place" along the edges of the road and settling on the pictographs: "You can see the deposition taking place" on the art.

Magnesium chloride is "vicious stuff," says Silver. "It peels concrete." Over time, she says, the salt will corrode the rock and damage the paintings on its surface.

But BLM managers familiar with Silver's study were hesitant about its conclusions. "Nine Mile is very controversial," says Roger Bankert, BLM field manager in the Price, Utah, office, who helped draft the soon-to-be-released EIS. "There could be extremist views on both sides. Some say there's a lot of damage, and some say there's no damage." Bankert suggested that additional analyses might be in the works. "We could have other specialists disagree with [Silver's report]," he said.

The use of magnesium chloride in Nine Mile Canyon as a dust suppressant has been "a concern for a long time" among some BLM staffers, says Dennis Willis, a BLM recreational planner in the Price office; some are also concerned that the salt is contaminating the canyon's stream. Although Silver's is the first study to suggest a magnesium chloride problem in Nine Mile, existing data suggest that the compound, also used as a road deicer, is a corrosive agent. Bankert points out that Carbon County supervises the use of the road, and county officials, not BLM, approved the magnesium chloride use.

Scientists familiar with the level of truck traffic on the canyon road say they are not surprised by Silver's findings. "The fact that the dust is being kicked up on the rock art panels is apparent to anyone who goes down there," says Kevin Jones, Utah's state archaeologist.

Some experts say it is inevitable that the dust buildup will cause damage. "Think of a painting in your house that is placed over a fireplace that produces soot," says chemist Marvin Rowe of Texas A&M University in College Station, who works on dating rock art. "Over time, that soot gets incorporated into the mineral content of the painting, and it builds a thick enough coating where it makes the painting fade away."

One option might be to wash the art, although some experts fear damage from washing, too. Silver predicts some action will be taken: "They're really going to have to do something about the road and clean up those sites."

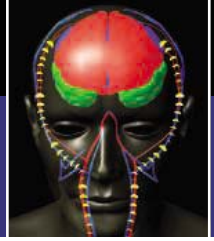
–KEITH KLOOR

Keith Kloor is a senior editor at *Audubon Magazine*.

Obscured. Once-vivid rock art panels like this one of a two-headed snake in Nine Mile Canyon (*top*) are shrouded by dust in 2006.

CREDIT: EARL IVAN WHITE

The end of the Quaternary?
402



An explosion of brain trauma
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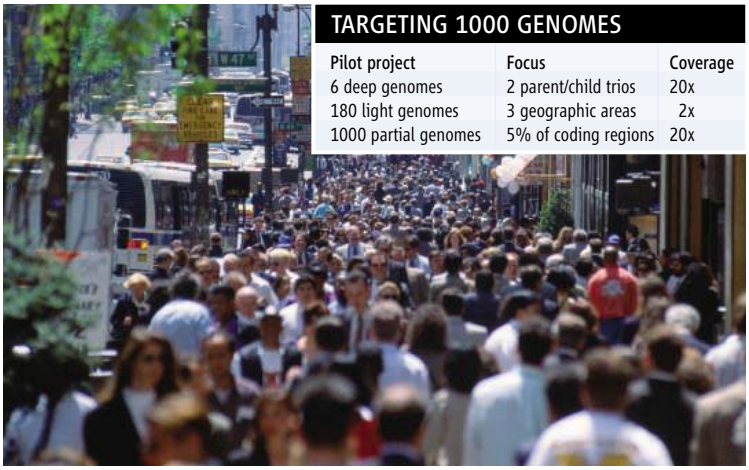
DNA SEQUENCING

A Plan to Capture Human Diversity in 1000 Genomes

It's sign of how fast horizons are changing in biology: Researchers who only a few years ago were being asked to justify the cost of sequencing a single human genome are now breezily offering to sequence 1000. And they say they can do it in a flash. Over the next 3 years, an international team plans to create a massive new genome catalog that will serve as "a gold-standard reference set for analysis of human variation," says Richard Durbin of the Sanger Institute in Hinxton, U.K., who proposed the project just last year.



TARGETING 1000 GENOMES

Pilot project	Focus	Coverage
6 deep genomes	2 parent/child trios	20x
180 light genomes	3 geographic areas	2x
1000 partial genomes	5% of coding regions	20x

More is better. Researchers aim to acquire DNA data from 1000 individuals.

The 1000 Genomes Project, as it's called, will delve much deeper than the sequencing of celebrity genomes, three of which were completed last year. It will help fill out the list of new genetic markers for common diseases that came out in 2007, says Francis Collins, director of the U.S. National Human Genome Research Institute (NHGRI) in Bethesda, Maryland. At the same time, new technologies will be put to the test, and researchers will work out how to handle a growing deluge of data. Such practical advances will be needed a few years from now when sequencing entire genomes will be routine, notes population geneticist Kenneth Weiss of Pennsylvania State University in State College, who is not part of the project. "This seems overall like a next logical step," he says.

The search for disease genes took off last year, building on the first human genome reference sequence in 2003 and the subsequent HapMap. The latter describes how blocks of DNA tagged by common variants, called single-nucleotide polymorphisms (SNPs), vary in different populations. These SNPs have turned up more than 100 new DNA markers associated with common illnesses such as diabetes and heart disease (*Science*, 21 December 2007, p. 1842). But the HapMap includes only the most common markers, those present in at least 5% of the population.

To find rarer SNPs that occur at 1% frequency, genome leaders say, they need to sequence about 1000 genomes. According to a plan hammered out by about three dozen experts last year, the project will take advantage of new technologies that have slashed the cost of sequencing. The work will be done by the three U.S. sequencing centers funded by NHGRI, the Sanger Institute, and the Beijing Genomics Institute (BGI) in Shenzhen, China.

Because the technologies are so new, the consortium will start with three pilot projects. One will exhaustively sequence the entire genome of six individuals: two adults and both sets of their parents. DNA in these six genomes will be analyzed repeatedly up to 20 times to ensure almost complete coverage. A second project will sequence 180 individual genomes at light (2×) coverage, leaving gaps. The third project will be to fully sequence (20× coverage) the protein-coding regions of 1000 genes (5% of the total) in about 1000 genomes. The samples, all anonymous and with no clinical information, will mainly be drawn from those collected for the HapMap, which includes people of European, Asian, and African descent.

The pilots should take about a year and will put the new technologies to a "very vigorous test," Collins says. After that, the consortium will decide what coverage to use to sequence the entire set of 1000 genomes. Most of the project's $30 million to $50 million price tag will be paid from the existing sequencing budgets of institutes, organizers say.

The new catalog could help disease gene hunters in several ways. It may allow researchers simply to hunt through an index for a SNP in a particular location that alters a gene product rather than run a time-consuming sequencing project, Collins says. The project will also catalog genes that are sometimes lost or duplicated; such copy-number variants can cause disease. By compiling rarer variants, it should also help resolve a debate about the relative contribution of these mutations to disease risks. "There's no question it's going to be a tremendous resource," says Yale University's Judy Cho, who has used the HapMap to find a new gene for Crohn's disease.

China is also launching its own human genomes project. BGI Shenzhen this month announced that it is seeking 99 volunteers who will help pay to have their genomes sequenced as part of a study of diversity (*Science*, 26 October 2007, p. 553). The 3-year effort, called the Yanhuang Project after the Yan and Huang tribes that are believed to be ancestors of modern Chinese, will overlap with the 1000 Genomes Project. With proper consent, some volunteers' genomes will be sequenced for both efforts, says Wang Jun, director of BGI Hangzhou.

In a parallel effort, J. Craig Venter of the J. Craig Venter Institute in Rockville, Maryland, says his team will sequence up to 10 individuals this year and publish the data along with medical information. Venter—who dismisses the 1000 Genomes Project as "more survey work" because not all genomes will be sequenced to great depth—has even bolder plans. He says he aims for "complete diploid genome sequencing" of 10,000 human genomes in the next decade. Still, he says, "it's great that there's such an expansion of things." **–JOCELYN KAISER**

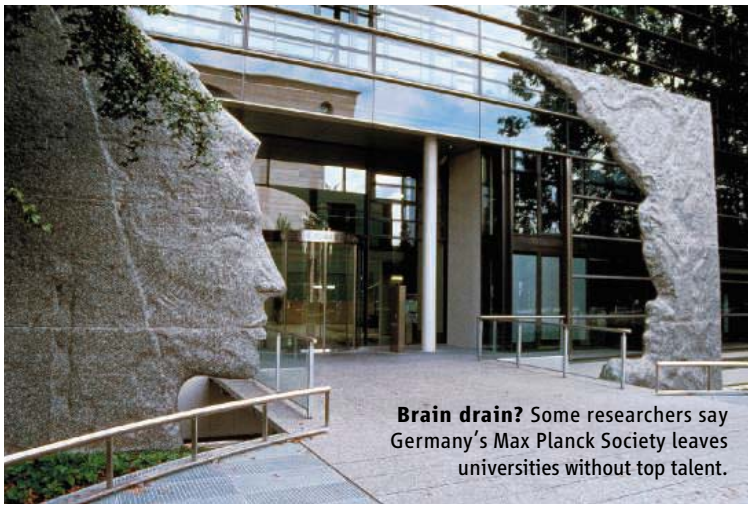
With reporting by Hao Xin.

CREDITS: (PHOTO) GRANT FAINT/GETTY IMAGES; (DATA SOURCE) NHGRI

GERMANY

Max Planck Accused of Hobbling Universities

International university rankings tend to give German schools an inferiority complex. In the latest worldwide assessment from Shanghai Jiao Tong University in China, no German university made it into the top 50. The government hopes to change that, pouring €1.9 billion ($2.8 billion) into an Excellence Initiative that is supposed to boost a few schools to world-class status (*Science*, 20 October 2006, p. 400). But this month, a group of respected researchers charged in a newspaper article that the problem isn't money, it's the country's Max Planck Society, which plucks many of the country's leading researchers out of universities into its own institutes. The missive has sparked a discussion in the press and the research community about how the country can best burnish its international reputation.



Brain drain? Some researchers say Germany's Max Planck Society leaves universities without top talent.

In an article headlined "The Unsolved Max Planck Problem," nine scientists, including Nobel laureate Günter Blobel of Rockefeller University in New York City, said that the Excellence Initiative is hopeless as long as the country's Max Planck Society skims off all the top talent. The scientists, writing in the 8 January *Frankfurter Allgemeine Zeitung*, said that Germany's two-tiered research system not only lures the best brains away from universities but also leads to a mismatch between the most promising graduate students and the best labs. They say the society's institutes should be merged into nearby universities, and its researchers should become professors with all the attendant privileges and responsibilities.

With its annual budget of €1.4 billion ($2.1 billion), the Max Planck Society funds 80 institutes, each focusing on a specific area in the natural or social sciences. Some institutes have just two directors—the position equivalent to a full professor—whereas the biggest has 10. Most are located in cities that have universities, and many do cooperate closely with local colleagues. Graduate students working in Max Planck labs, for example, must be enrolled in a partner university, from which they receive their degree. But too often, says Widmar Tanner, a biologist at the University of Regensburg who initiated the article, Max Planck Institutes and universities are in direct competition. "The elite university programs cannot work as long as you have this competitive structure called the Max Planck," he says.

The training of Germany's young talent also suffers, say Tanner and his co-authors. Although some Max Planck researchers do teach, their contact with students is less than a university professor would have. That leads to a disconnect between the most promising young researchers and top mentors, the authors charge. The problem is exacerbated, they say, because Germany has no standardized test like the American Graduate Record Examination, so graduate students are largely recruited through personal contacts. Without the personal contacts, Max Planck researchers are at a disadvantage when hiring. Max Planck labs "get very good postdocs, but the young, fresh graduate students? At best average," Tanner says.

The solution, the authors say, would be to integrate Max Planck institutes into their local universities, adopting a system more like that of the Howard Hughes Medical Institute in Chevy Chase, Maryland, where selected researchers receive extra funding but remain employed by their host university—and lend it their renown. Such ideas have been proposed before, the authors acknowledge. They even quote Nobel laureate Max Delbrück criticizing the Max Planck's forerunner, the Kaiser Wilhelm Society, "because it takes the best people out of teaching and impoverishes contact with students." Even so, Tanner says, criticism of the Max Planck today "is taboo" in German political circles. "We wanted to start a discussion," he says.

The authors "may have good intentions, but [their proposal] is not the solution," says Max Planck President Peter Gruss. The numbers just don't add up, he says. The society's 260 directors "will not suffice to change the university system," and the society's entire budget is less than that of Stanford University—often cited in Germany as the kind of elite school the country lacks.

"Those who desire integration do not comprehend the concept of a Max Planck institute," Gruss says. The society's purpose is to be flexible enough to fund cutting-edge research across all fields, and its institutes are ultimately temporary. "When I was a student studying virology, Max Planck closed a virology institute in Tübingen and opened one in developmental biology. Thank God we did, because we got Christiane Nüsslein-Volhard to work there." In 1995, Nüsslein-Volhard won the Nobel Prize in physiology or medicine. "We try to get the best person in a given field. If we don't get the best person, we change direction and find a new field." A university does not have the same freedom to drop old fields and pick up new ones, he says. Merging Max Planck into universities would "remove a successful system that by any measure is in the top tier of institutes worldwide."

Gruss and others point out that the Excellence Initiative has encouraged new cooperation between universities and Max Planck. Most of the schools that won funding in the nationwide competition did so by developing so-called Centers of Excellence or Graduate Colleges that bring together researchers from the university and a neighboring Max Planck institute. The programs "have broken down the alleged divisions and led to many close collaborations that play on the strengths of both partners," says Matthias Kleiner, president of Germany's main funder of research grants, the DFG.

German universities that want to make themselves world-class can learn from another of Max Planck's key strengths, Gruss says: "What you need to do is to give some people more and take it from others. The universities over the last decades were not prepared to do that." **–GRETCHEN VOGEL**

CREDIT: WOLFGANG FILSER/MPG

EDUCATION

France Launches Public Health School *à l'Anglo-Saxonne*

RENNES, FRANCE—If imitation is the sincerest form of flattery, schools of public health in Britain and the United States should feel pleased. France has just created a new institute, the first of its kind in France, that takes its inspiration from the Harvard School of Public Health, the London School of Hygiene and Tropical Medicine, and other famous Anglo-Saxon institutes. Its goal: to give France, currently a bit of a laggard in public health research and education, an institute that can compete with the world's best.

The new French School of Advanced Studies in Public Health (EHESP) holds some trump cards: strong political backing, a new master's degree in English to lure anglophone students and teachers, and a dream location in the heart of Paris, next to the Notre Dame cathedral. But some experts say making it a success remains an uphill climb.

Many countries in continental Europe don't have a tradition of public health schools separate from the faculty of medicine. In contrast, there are 40 in the United States. Public health expertise is particularly scattered in France, says Jacques Bury, a former director of the Association of Schools of Public Health in the European Region who now works for a private consulting company in Geneva, Switzerland.

To address that situation, France passed a public health law in 2004 that ordered EHESP into existence. It doesn't start from scratch, however. Officially opened this month, the school is an evolution of the National School of Public Health, an "école d'administration" with a €57 million annual budget, in Rennes, 400 kilometers west of Paris. For the past 45 years, it has trained managers and inspectors for France's state-run health care system. The new school—the law gives it the status of a university—will continue that mission but add master's and Ph.D. programs and dramatically expand its research in areas such as epidemiology, information sciences, and health care management, says EHESP dean Antoine Flahault. The existing school, whose research focuses on environmental health and social sciences, will morph into two of EHESP's five departments.

New construction is planned for the Rennes campus to accommodate those plans. In addition, Flahault has convinced the city of Paris to give EHESP an entire floor in the Hôtel-Dieu, a legendary hospital that occupies "one of the 10 best addresses in the world," says Flahault. Putting the master's program there should help lure top talent, he says.

Flahault, 47, an expert in infectious disease modeling at Pierre and Marie Curie University in Paris, is an unabashed admirer of the Anglo-Saxon schools. He plans to apply for accreditation from the U.S. Council on Education for Public Health in Washington, D.C., which so far has accredited only one non-U.S. school. That would be a way to assure that EHESP is doing its job well, and it might help persuade U.S. students and staff to come to France, he says.

CREDIT: SERGE CANNASSE

Grand ambitions. Dean Antoine Flahault wants the new public health school to compete with the world's best.

Making the school compete in research at the international level will be a challenge, however, says Yves Charpak, a former policy officer at the World Health Organization who now heads international affairs at the Pasteur Institute in Paris. EHESP does not have a big purse to recruit outsiders; the government, which strongly supports the school, has promised Flahault 12 new professorships, but to become a true science powerhouse, EHESP will need to draw in research teams from universities and institutes such as the biomedical research agency INSERM, which have their own agendas.

But Flahault is optimistic that the new school will become a magnet. And he hopes to tap other sources of money as well, such as endowed professorships—yet another Anglo-Saxon idea that he plans to copy.

–MARTIN ENSERINK

Election '08 Moves Online

Scientific groups are working hard to bring their issues before the U.S. presidential candidates. Going live last week was sciencecures.org, funded by the Federation of American Societies for Experimental Biology, which offers letter-writing tools and advocacy materials. Also this month, AAAS (which publishes *Science*) launched election2008.aaas.org, which examines where the candidates stand. Then there's the richly sourced Science, Health And Related Policies (sharp.sefora.org) Network, from Scientists and Engineers for America, with links to voting records and a wiki for readers to contribute.

Meanwhile, a campaign by science journalists and academics for presidential science debates has picked up the endorsement of the chair of the House Science Committee, Representative Bart Gordon (D–TN). But David Goldston, former chief of staff to Gordon's predecessor as committee chair, Representative Sherwood Boehlert (R–NY), worries that a debate could "politicize" the issues and even prompt some candidates to oppose more funding for research. **–ELI KINTISCH**

Judge Modifies Sonar Ruling

A U.S. judge has decided that silence is not golden for marine mammals. Last week, District Judge Florence-Marie Cooper temporarily suspended some restrictions she had placed on the Navy's use of mid-frequency active (MFA) sonar, continuing the legal battle over a series of antisubmarine warfare exercises off the southern California coast.

Cooper acted 2 days after the Bush Administration granted the Navy waivers from two environmental laws covered under her 3 January ruling. MFA sonar has been linked to strandings of marine mammals, and environmental groups brought suit last March to force the Navy to limit its use in the exercises. Cooper's most recent ruling suspended her previous order that the Navy maintain a 2000-meter marine mammal "safe zone" around sonar sources and restrict the system's power under certain conditions. Other restrictions remain intact, however, including a 22-kilometer-wide no-sonar zone along the California coast.

The latest development is "a step backward," says Linda Weilgart, a bioacoustician at Dalhousie University in Halifax, Canada, who gave expert testimony in the case. Cooper herself had called the Navy's own plans, which are similar to what the waivers allow, "grossly inadequate." More briefs are due this week, and whichever side loses the next ruling is expected to appeal. **–BENJAMIN LESTER**

SCIENCE STATISTICS

Got Data Questions? NSF's *Indicators* Has (Most of) the Answers

Few would argue with Steven Beering, chair of the oversight board for the U.S. National Science Foundation, when he asserts that NSF's biennial *Science and Engineering Indicators* represents "the most authoritative source of information on international trends in science and technology." The data-packed, two-volume 2008 report issued last week (www.nsf.gov/statistics/seind08/) would be just the place to go if the makers of Trivial Pursuit come out with a special science policy edition. But it's also a good source for politicians and lobbyists as they debate everything from training the next generation of scientists to the trade balance in high-tech manufactured products.

Drawing on the myriad studies, surveys, and analyses that make up this year's *Indicators*, *Science* offers a few facts that, given the tenor of those debates so far, may come as a surprise to readers.

–JEFFREY MERVIS

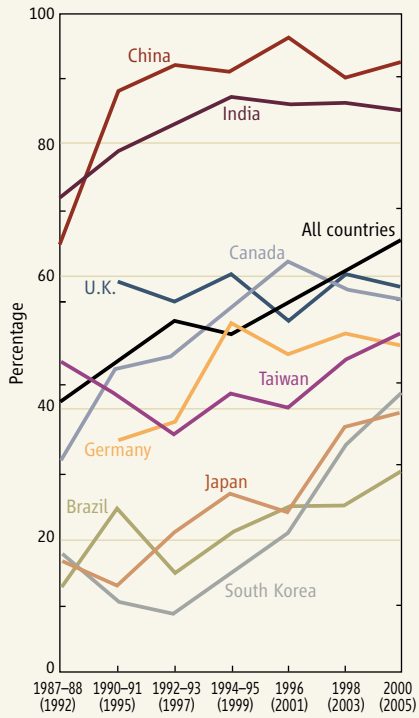
SOME THINGS WE KNOW

Are tenure-track academic positions really an impossible dream for newly minted U.S. science and engineering (S&E) Ph.D.s?
Indicators notes that "in recent years, the proportion of all recent doctoral recipients who are in tenure-track academic jobs has increased" (fig. 3-33; see graph). What's more, the share of recent Ph.D.s in mathematics and computer science holding tenure-track posts has rebounded sharply since a dip in 2001. (Overall, 26% of S&E Ph.D.s were in tenure-track positions 4 to 6 years after receiving their doctorates.)

Are more and more foreign-born graduate students really heading home after receiving their U.S. doctoral degrees?
In reality, "stay rates" for this large and desirable pool of talent are rising (fig. 3-65; see graph) despite the global expansion of the scientific work force. For example, close to 90% of the Chinese- and Indian-born students who earned their Ph.D.s in 2000 were still in the United States in 2005.

Are today's U.S. college students really less interested in S&E than previous generations?
In fact, the percentage of first-year students who say they intend to major in S&E fields has remained constant for the past 2 decades (appendix table 2-15). And overall, that interest doesn't flag during college: The percentage of degrees awarded in S&E fields is slightly higher than the percentage of students declaring their interest as freshmen. That's because the number of students entering S&E programs more than offsets those who leave for other fields (table 2-6; see graph).

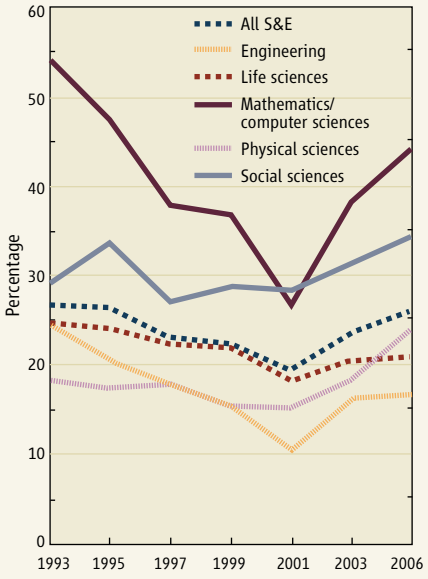
Still in the U.S.



Global citizens. Those with temporary visas are increasingly likely to remain in the United States 5 years after earning their S&E Ph.D.s, according to Michael Finn of Oak Ridge Institute for Science and Education. The already high rates for Chinese- and Indian-born students have risen during the past 2 decades.

SOURCE: M. FINN, OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION (2007)

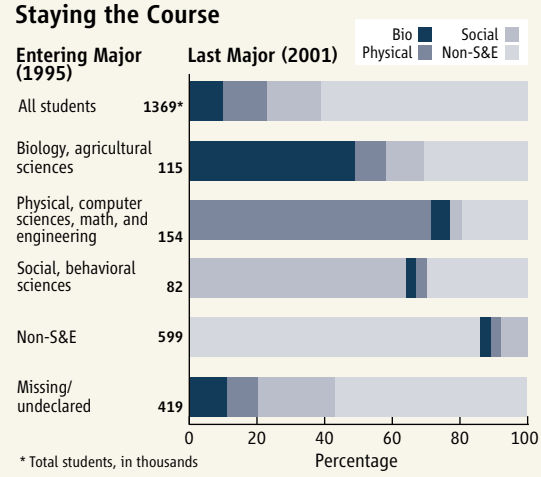
Riding the Tenure Track



Bouncing back. NSF's survey of doctoral recipients finds that scientists who earned their Ph.D.s 4 to 6 years earlier are having more success in obtaining tenure and tenure-track positions.

SOURCE: NSF

Staying the Course

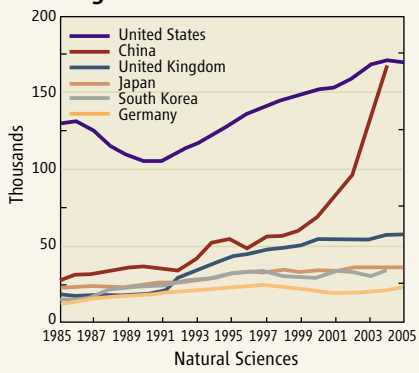


Major decisions. A majority of first-year U.S. undergraduates declaring S&E majors in 1995 stuck with it through graduation, according to a study that followed that cohort. The relative balance varies greatly by field: the agricultural and biological sciences are the most fluid and the physical sciences the least. Significantly, the numbers of those who shifted into non-S&E fields were more than offset by those entering S&E fields.

SOURCE: NCES, 2001 BEGINNING POSTSECONDARY STUDENTS LONGITUDINAL STUDY, 2007

SOURCE: *SCIENCE AND ENGINEERING INDICATORS 2008*

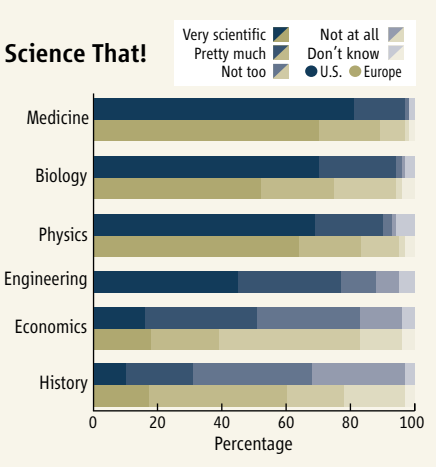
Are developing economies exceptional in cranking up their output of S&E graduates?
China's remarkable expansion of its higher education system has captured the most attention, and its sixfold increase in the number of undergraduate natural science and engineering (NS&E) degrees in the past 20 years is indeed a shocker (fig. 2-35; see graph). But South Korea and the United Kingdom have both nearly tripled their yearly output of first university NS&E degrees since 1985. And even in the United States, with the largest supply, the number of NS&E bachelor's degrees has grown by 31%. (Significantly, that pool is almost entirely domestic. Students on temporary visas receive only 4% of U.S. S&E bachelor's degrees.) At the same time, experts have raised questions about how China's rapid expansion has affected the quality of the education being offered, an issue that is much harder to quantify (*Science*, 11 January, p. 148).



The naturals. The natural sciences—biology; mathematics; and earth, ocean, agricultural, computer, and physical sciences—are still popular majors for undergraduates around the world, with China poised to overtake the United States in the absolute number of degrees awarded.

SOURCES: RELEVANT GOVERNMENT AGENCIES IN CHINA, GERMANY, JAPAN, UNITED KINGDOM, UNITED STATES; OECD

Does Albert Einstein really represent the quintessential scientist to the average adult?
Although the patent clerk from Bern may be the most recognizable face in the world of science, two recent surveys (table 7-12, fig. 7-13; see graph) found that people think physicians, not physicists, are in the "most scientific" field of study. Medicine was the clear favorite among both Europeans and Americans, well ahead of its companion field of biology and also outdistancing physics and engineering. The social sciences trail the pack, with Europeans naming history as the least scientific among five fields and Americans ranking it behind accounting in an eight-field race.



Call a doctor. Americans and Europeans, in separate surveys covering similar disciplines, agree that medicine is the "most scientific" of fields. (Europeans were not asked about engineering, accounting, or sociology; Americans ranked the latter two sixth and last, respectively, among eight disciplines.)

SOURCES: UNIVERSITY OF CHICAGO, NORC, GENERAL SOCIAL SURVEY, 2006; EUROPEAN COMMISSION, EUROPEANS, SCIENCE & TECHNOLOGY, 2005

WHAT WE DON'T KNOW

For the first time, the National Science Foundation staff that compiles and writes *Indicators* confessed in print that there are lots of questions about the state of the S&E enterprise that its authoritative tome doesn't answer. The main reason, says Rolf Lehming, who oversees the volume, is that the data just don't exist or aren't reliable. "Collecting high-quality data can be exceedingly expensive, and governments cannot afford to collect all they could use productively," he writes.

Some topics for which data are lacking:

• Education and training: Informal learning experiences, from online courses to zoos; how math and science teachers are trained and their career paths; how to track emerging fields and multidisciplinary programs; how to compare curricula around the world;

• Across the labor force: The global flow of S&E workers; lifelong learning and employer training programs;

• R&D trends: The characteristics of research-intensive businesses; research outside academia, the federal government, and large companies; the outsourcing and offshoring of S&E jobs.

SOURCE: *SCIENCE AND ENGINEERING INDICATORS 2008*

Bearing Down on Oil Drilling

A leading Democratic legislator wants the U.S. Department of the Interior (DOI) to delay the sale of drilling rights in polar bear habitat until its Fish and Wildlife Service (FWS) decides whether to add the species to its endangered species list. Last year, FWS proposed listing the polar bear within 12 months, because rising temperatures are melting the sea ice it uses for habitat (*Science*, 5 January 2007, p. 25). After the agency said earlier this month that it couldn't meet the statutory deadline, environmentalists sued. Meanwhile, DOI's Minerals Management Service plans on 6 February to auction the rights to drill in prime polar bear habitat in Alaska's Chukchi Sea. Legislation proposed last week by Representative Edward Markey (D–MA), chair of the Select Committee on Energy Independence and Global Warming, is meant to let DOI know "how serious the chairman is," says an aide.

–ERIK STOKSTAD

Hubble Trouble

Space shuttle delays could postpone the August mission devoted to repairing and upgrading the Hubble Space Telescope, NASA science chief S. Alan Stern warned last week. Technical problems last month forced the space agency to delay launch of the orbiter carrying the European Space Agency's Columbus module to the international space station until early February. That has backed up other space station assembly missions, including the three required to put Japan's module in orbit. An extended hold on Hubble repairs worries project managers, who note that some of the telescope's aging systems are on their last legs. NASA has promised to retire the shuttles and complete the station by 2010.

–ANDREW LAWLER

China Reaches Dome A

BEIJING—A 17-person team led by the Polar Research Institute of China last week struck camp at the highest bulge on the East Antarctic Ice Sheet in search of the best astronomical viewing on Earth. The team is installing an automated suite of instruments to measure atmospheric turbulence, moisture, and other parameters and is setting up four 14.5-centimeter optical telescopes that will start snapping images after night falls in March. "Everything is going smoothly," says Cui Xiangqun, an astronomer at the Nanjing Institute of Astronomical Optics and Technology, which built the telescopes. China hopes to have a year-round base at Dome A up and running by 2010.

–RICHARD STONE

ASTROPHYSICS

"Little" Cosmic Ray Observatory Aims to Make a Big Mark

In a field in which bigger is usually better, what can you hope to achieve with a new experiment that's only a quarter as large as its well-established rival? Plenty, say 117 physicists mainly from Japan and the United States who have just started taking data with a cosmic ray observatory that covers 730 square kilometers of western Utah.

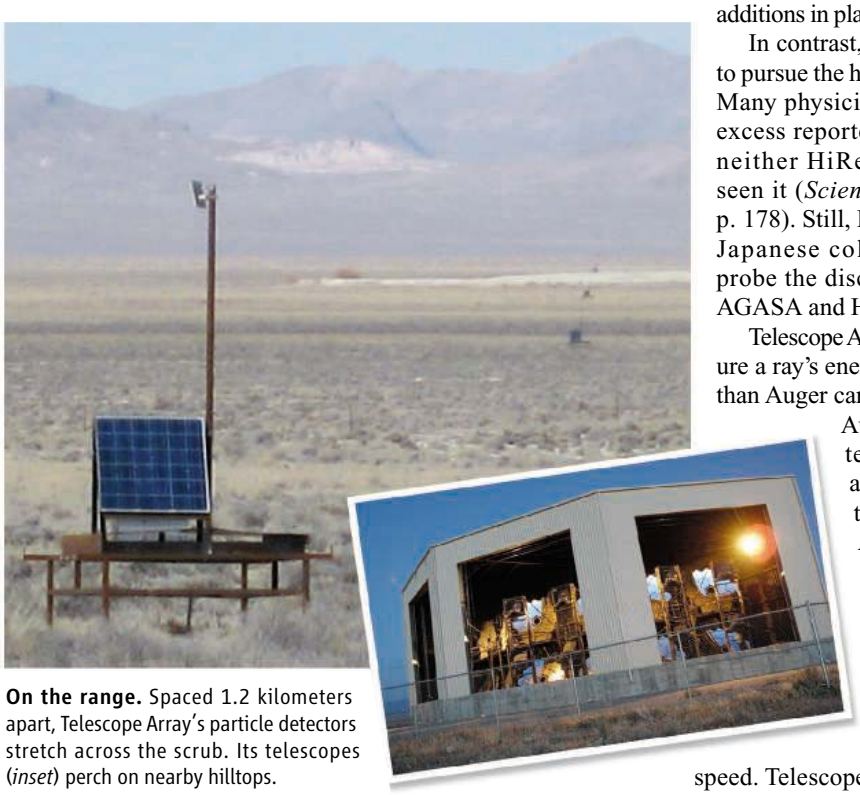
Dubbed Telescope Array, the observatory aims to spot the most energetic subatomic particles from space. Such ultrahigh-energy cosmic rays pack as much energy as a golf ball hitting a fairway, and they strike Earth at a rate of 1 per century per square kilometer. Interest in them grew 10 years ago, when Japanese physicists reported an odd excess of the highest energy rays. It surged last year, when the gargantuan Pierre Auger Observatory in Argentina traced the rays to certain galaxies (*Science*, 9 November 2007, p. 896).

Telescope Array aims to test the Auger result and to decipher the nature of the rays. It enters the fray as an underdog: Although it's bigger than the city of Chicago, it's only a quarter the size of Auger, which has been taking data since 2004. But team members say Telescope Array has key technological advantages, and others say it may be better for pursuing certain questions. "This is a very important experiment," says Veniamin Berezinsky, a theorist at Gran Sasso National Laboratory in Assergi, Italy.

The Telescope Array collaboration formed when two rival groups merged. Physicists measure the energies of cosmic rays in exa–electron volts, and in 1998, researchers with the Akeno Giant Air Shower Array (AGASA) near Tokyo reported seven rays with energies above 100 EeV. By 2002, they saw 11. That was about 10 times more than expected; if the rays were protons, then on average, interactions with the cosmic microwave background should have sapped their energy to 60 EeV before they had traveled 200 light-years.

Some theorists took the excess as evidence that the rays were born in decays of exotic particles lingering nearby. But physicists with the High Resolution Fly's Eye (HiRes) detector in Dugway, Utah, argued that there was no excess: They saw only two such rays. The HiRes and AGASA groups studied the rays using different techniques, however. So to resolve the discrepancy, they eventually decided to build an array that would use both.

When a cosmic ray strikes the atmosphere, it sets off an avalanche of particles called an extensive air shower. AGASA sampled the shower using 111 particle detectors spread over 100 square kilometers. The shower also causes the air to fluoresce, and HiRes studied that light using twin batteries of telescopes. Telescope Array comprises 503 particle detectors and 38 telescopes in three batteries.



On the range. Spaced 1.2 kilometers apart, Telescope Array's particle detectors stretch across the scrub. Its telescopes (*inset*) perch on nearby hilltops.

CREDITS: MASAKI FUKUSHIMA AND SHIGEHARU UDO (INSET)/INSTITUTE FOR COSMIC RAY RESEARCH, UNIVERSITY OF TOKYO

Japan put up $13 million for the $16 million array, but researchers never considered constructing it there. "Building a fluorescence detector in Japan is impossible," says Masaki Fukushima of the University of Tokyo. "Because of the humidity, the transparency of the air is very limited." The project got its inapposite name because the Japanese had previously proposed an array of 10 telescopes with no particle detectors. "Once you propose something you don't change the name, because no one will know what you're talking about," says Pierre Sokolsky of the University of Utah, Salt Lake City. "So even though it makes no sense, the name stuck."

Because it's bigger, Auger will see more of the rare rays above 60 EeV. So Sokolsky plans to focus on lower energies and especially on a kink in the spectrum of rays near 4 EeV that might mark the point at which rays from within our galaxy peter out and those from beyond take over. The team has proposed a "low-energy extension" of 100 more-tightly-spaced detectors and two more telescope stations to measure showers with between 0.03 EeV and 10 EeV. "For this, the Telescope Array and especially the low-energy extension is an excellent instrument," Gran Sasso's Berezinsky says. Auger should have similar additions in place in 2009.

In contrast, Fukushima hopes to pursue the highest energy rays. Many physicists now doubt the excess reported by AGASA, as neither HiRes nor Auger has seen it (*Science*, 13 July 2007, p. 178). Still, Fukushima and his Japanese colleagues hope to probe the discrepancy between AGASA and HiRes.

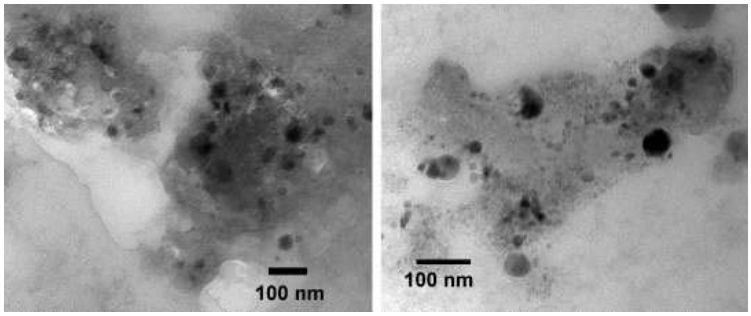
Telescope Array will also measure a ray's energy more precisely than Auger can, Fukushima says. Auger comprises four telescope batteries and nearly 1500 particle detectors. But Auger's detectors are of tanks of water, which produces light called Cherenkov radiation when a particle zips through it at near-light speed. Telescope Array's detectors are sheets of plastic scintillator that emit light through another mechanism. "Definitely we are measuring the cosmic rays in a different way and with better energy resolution," Fukushima says.

Ultimately, Auger and Telescope Array may be forced to work together. The Telescope Array team hopes someday to expand its observatory, and the Auger team plans to build a far-bigger array in Colorado in a few years. The two arrays could end up being combined, Sokolsky says. "Whatever we scientists might think about it, that's going to be imposed on us by the funding agencies," he predicts. For now, however, the competition is on. **–ADRIAN CHO**

GEOCHEMISTRY

Where Has All the Stardust Gone?

Surprise has followed surprise for cosmochemists analyzing the dust sample that the Stardust spacecraft returned from comet Wild 2 in January 2006. First, they found tiny flecks of once-molten minerals—material very different from the raw, primordial dust they expected to see. Such unaltered, so-called presolar material was the prime ingredient of the rocky planets and was thought to abound in icy comets. But on page 447, researchers report that they have failed to find a single speck of it.



An unfortunate match. Globs of mineral-riddled glass (*left*) from a comet sample were created during sample collection, as replicated in the lab (*right*).

"For those of us who study presolar materials, it's turned out to be a bit of a bust," says cosmochemist Larry R. Nittler of the Carnegie Institution of Washington's Department of Terrestrial Magnetism in Washington, D.C. "Wild 2 seems more related to asteroids than comets," because all asteroids were altered from the solar system's primitive starting materials. Still, "the mission's been a huge success," says John Bradley of Lawrence Livermore National Laboratory (LLNL) in California, a co-author of the *Science* paper. "It's changing the way we think about comets."

Before Stardust's return, cosmochemists thought of comets as vaults where the primitive ingredients of the planetary recipe had been locked up. Their best look at the likely ingredients list came from the study of certain meteoritic particles collected in Earth's stratosphere by retired spy planes. Because of their exotic isotopic composition, these particular interplanetary dust particles (IDPs) looked as though they might be comet dust. Presumably, such primitive dust fell into the cold, outer reaches of the nebula that gave rise to the planets and combined with nebular ices to form comets, in which the dust has been preserved ever since.

One of the unaltered components of cometlike IDPs was so-called GEMS (glass with embedded metal and sulfides). And early analyses of particles captured near Wild 2 by Stardust tantalizingly revealed GEMS-like particles. But cosmochemist Hope Ishii of LLNL and her colleagues report in this issue that the GEMS-like particles in Stardust samples were actually forged as Wild 2 dust particles plowed into the wispy glass of the Stardust sample collector at a blistering 22,000 kilometers per hour. The researchers made some themselves by shooting mineral particles into collector material at Stardust velocities. Stardust principal investigator Donald Brownlee of the University of Washington, Seattle, does allow that any true GEMS—which tend to be submicrometer in size—might have been lost on impact with the Stardust sample collector.

Ishii's group also found only one microscopic "whisker" of the mineral enstatite. Such threadlike crystals are common in primitive, cometlike IDPs, but the lone Stardust find has the wrong orientation to have come from a comet. And what little organic matter could be found in the Stardust sample has a much lower deuterium-hydrogen ratio than the organic matter of cometlike IDPs.

All in all, "it's looking as if Wild 2 is more like an asteroid than a primitive comet," says Ishii. Brownlee agrees. Rather than preserving the original ingredients of planets, comets—or at least Wild 2—seem to be loaded with materials first altered by the great heat near the young sun, he says. Then those altered materials must have been carried outward to the outer reaches of the nebula, where comets incorporated them. "I would say a large fraction of the [outermost] nebular materials were probably transported there" from much nearer the sun, Brownlee says, "which is pretty amazing." Now, no one is at all sure where the solar system's lingering primitive materials might reside.

–RICHARD A. KERR

HISTORY OF SCIENCE

Dutch Universities Split Over Nobel Laureate's Rehabilitation

AMSTERDAM, THE NETHERLANDS—Allegations that the late Dutch physicist Peter Debye was cozy with the Nazis before and during World War II have produced a split decision among schools who once honored him. Following the advice of an independent committee, Utrecht University last week exonerated the Nobelist by restoring the name of its Debye Institute for NanoMaterials Science. But Maastricht University, in Debye's hometown, rejected the advice and removed his name from a scientific prize permanently.

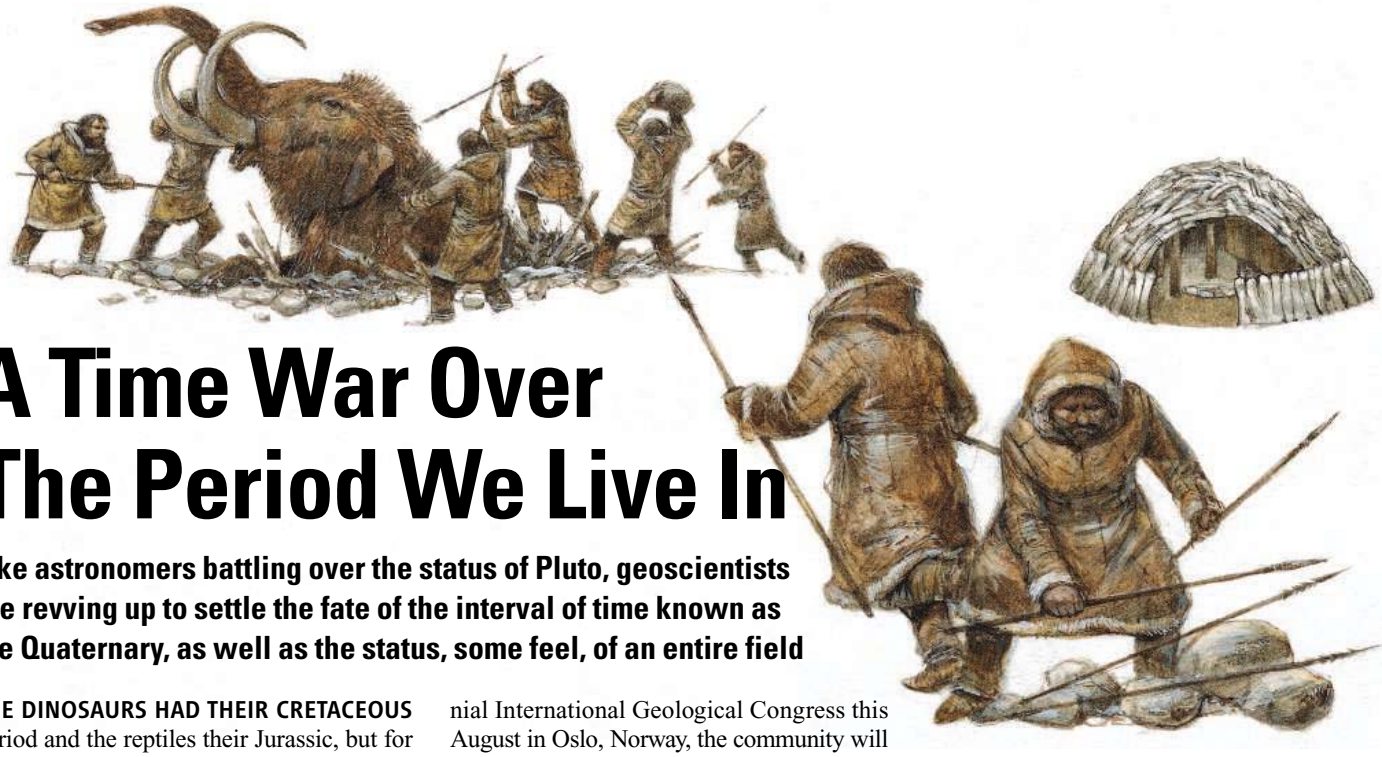
Both universities dropped Debye's name after a book and a magazine article by journalist and science historian Sybe Rispens charged that Debye had "dirty hands" during and after his 1934–1939 stint as director of the Kaiser Wilhelm Institute for Physics in Berlin. Debye asked Jewish members of the German Physical Society to step down in a 1938 letter, for instance. Although not disputing the letter, Debye's defenders said he was neither an anti-Semite nor a Nazi sympathizer but an apolitical figure mainly interested in science (*Science*, 30 June 2006, p. 1858).

In November, a 200-page study by Martijn Eickhoff of the Netherlands Institute for War Documentation, which called Rispens's portrayal of Debye a "caricature," offered a nuanced picture of the scientist. It said Debye had a "survival mechanism of ambiguity." Based on that report, a committee set up by the two universities and chaired by physicist and politician Jan Terlouw concluded on 17 January that there's "no evidence of bad faith" on Debye's behalf, and that the institutes should reinstate his name. But in a statement, Maastricht University insisted that Debye's role remains "irreconcilable" with an award.

To Mark Walker, a historian at Union College in Schenectady, New York, who specializes in science in the Nazi era, that is an unsatisfactory ending. "I think the whole affair is unfair to Debye's memory," he says. "He acted according to his standards. They weren't the standards of a hero, but they weren't that bad."

–MARTIN ENSERINK

CREDIT (LEFT TO RIGHT): H. A. ISHII *ET AL.*, *SCIENCE*



A Time War Over The Period We Live In

Like astronomers battling over the status of Pluto, geoscientists are revving up to settle the fate of the interval of time known as the Quaternary, as well as the status, some feel, of an entire field

THE DINOSAURS HAD THEIR CRETACEOUS period and the reptiles their Jurassic, but for 200 years now, humans have not agreed on what period of geologic time we are living in. It could be the Neogene period. On many geologic time scale charts, the Neogene runs from 23 million years ago to the present. Or it could be the Quaternary. "The Quaternary is the most important interval of geologic history," says John Clague, former president of the International Union for Quaternary Research (INQUA). On some charts, the Quaternary spans the last couple of million years of time, including when humans took up tools and the world began slipping into icy climatic gyrations.

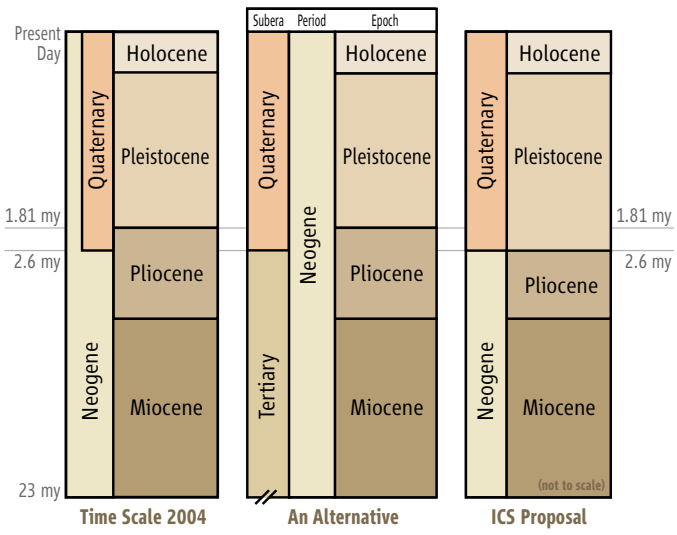
Depending on the time scale considered, the Quaternary sometimes takes a position of pride following the Neogene period. But other times it's relegated to sideshow status, and sometimes it's even absent entirely. Indeed, in recent years, the International Commission on Stratigraphy (ICS) "abolished" the Quaternary, according to riled quaternarists. "They tried to suppress it while no one was looking," says Philip Gibbard of the University of Cambridge in the U.K. "They nearly got away with it, [but] we were not going to have it." The Quaternary "is a manifestation of our community," adds Clague. "We don't want anyone denigrating that."

Now these geoscientists are heading for a showdown over the Quaternary. At the next quadrennial International Geological Congress this August in Oslo, Norway, the community will consider an ICS proposal that would enshrine the Quaternary as a full-fledged period encompassing 2.6 million years expropriated from the young end of the Neogene. But there are rules for dividing up time, notes marine geologist William Berggren of Rutgers University in Piscataway, New Jersey—rules that yield a consistent and therefore useful common language among geologists. And the quaternarists aren't following them, he says. "This is not going to happen."

A matter of time …

Geologists have divvied up time for the sheer convenience of it ever since the late 18th century, when they began to realize just how much of it there was, but the formal rules for dividing the geologic time scale started emerging only in the mid–20th century. Most fundamentally, the divisions must be hierarchical—a whole number of the smallest units of time constitute a single unit at the next higher level, and so on. And the boundaries between units must be recognizable worldwide, not just at a few special places. Conflicts between such modern rules and divisions that evolved over centuries linger into the early 21st century.

The Quaternary came into usage 2 centuries ago as the most recent of four divisions of the fossil record of life: the Primary, Secondary, Tertiary, and Quaternary. Geologists generally used Quaternary to refer to the loose soil and sediment moved around by the glaciers of the ice ages. That sediment held a distinctive set of fossils, living representatives of which are still common. But, Primary and Secondary fell out of use long ago, supplanted by other names. In recent decades, ICS—with the consent of the International Union of Geological Sciences (IUGS), the world's ruling body on such matters—dropped the Tertiary as well. Now, the Quaternary name "doesn't make any sense," concedes Norman Catto of Memorial University of Newfoundland in St. John's and



Take your pick. The Quaternary has been variously portrayed in a secondary status (*left*), as a subera (*middle*), and as a period (*right*).

CREDITS (TOP TO BOTTOM): RICHARD HOOK/GETTY IMAGES; SOURCE: MODIFIED FROM A GEOLOGIC *TIME SCALE 2004*; M.-P. AUBRY *ET AL.*, EPISODES 28, 1 (JUNE 2005); ICS PROPOSAL TO IUGS

The real quaternarists. Study of the Quaternary includes the environment of early humans.

editor-in-chief of *Quaternary International*. "It's the fourth division of a system in which the other three divisions have been thrown out."

The Quaternary may be a lingering anachronism, but "the name is less important than the concept," says Catto. "We have the strong [early] human element involved. That sets it apart. And it's defined as a time of glaciation." Indeed, many INQUA researchers are, strictly speaking, not geologists but anthropologists, climatologists, glaciologists, or paleoecologists, he says, specialists who are not attuned to the niceties of the modern geologic time scale.

Even as the term "Quaternary" was coming into use, however, another, slightly different interval of time with a different name was also becoming identified with the ice ages. In 1839, a founder of modern geology, Charles Lyell, dubbed what turned out to be the past 1.8 million years the Pleistocene ("most recent"). He defined the interval on the basis of a distinctive set of fossil mollusks; many of those species are still around today.

But unlike the Quaternary, Lyell's Pleistocene eventually became firmly incorporated in the emerging, official geologic time scale. In 1983, after 35 years of dickering in the community, a joint INQUA-ICS working group defined the beginning of the Pleistocene as that point in an outcrop of marine sediment at Vrica in southern Italy where several species of microfossils make their first or last appearance in the geologic record. Earth's magnetic field flipped about then, too; the reversal is recorded in the sediments around the world. The community drove the "golden spike," as the marker of a geologic boundary is called, at Vrica because its fossil transitions could be recognized far beyond Italy. Geologists working around the world could tell just where in the geologic record they were.

… or perspective

For the next decade or two, the Quaternary languished in the shadow of the Pleistocene. IUGS had ratified the golden spike at the beginning of the Pleistocene "isolated from other more or less related problems, such as … the status of the Quaternary," as the formal IUGS announcement put it in 1985. And INQUA "was sleeping" through the 1990s, says Gibbard. He would soon change that.

In December 2001, Gibbard heard that a major scientific publication then in the works—*A Geologic Time Scale 2004*, 600 pages long, with 40 contributors, and co-sponsored by ICS—would give the Quaternary short shrift. In the book's accompanying wall chart, the Neogene period and its youngest subdivision—the Pleistocene epoch—reigned supreme. The Quaternary made just one appearance, on a separate plot of the comings and goings of the ice ages. It lost out because "partly to our surprise, it had no official rank [in the hierarchy] or length," says James Ogg of Purdue University in West Lafayette, Indiana, who prepared the chart with Felix Gradstein of the University of Oslo, Norway.

Although the time scale had no official scientific standing, Gibbard sprang into action. At his instigation, "INQUA said to IUGS we weren't going to take it from ICS," Gibbard says. "ICS were told in no uncertain terms by IUGS they couldn't ignore the Quaternary community." In response to the fracas, IUGS President Zhang Hongren of Beijing withheld IUGS's 2007 funding for ICS until ICS properly addressed the Quaternary problem.

"The rest of the community is going to ignore" the Quaternary.

—WILLIAM BERGGREN, RUTGERS UNIVERSITY

"They tried to suppress [the Quaternary] while nobody was looking."

—PHILIP GIBBARD, UNIVERSITY OF CAMBRIDGE

And address the problem it did. "Now I think we've reached a pretty good compromise," Ogg says. "We hope so." The proposal gives the last 2.6 million years of the Neogene to an official Quaternary period, beginning about when world ocean circulation shifted and climate swings intensified in a cooling world. "We won a battle," says Clague. "It goes beyond a name. It's about how people working in the Quaternary are perceived."

To follow the rules, some cutting and pasting of the time scale will be required. In order to line up the beginning of the Quaternary with the beginning of the Pleistocene and thus maintain a proper hierarchy, an 800,000-year slice of the earlier Pliocene epoch will have to move up into the Pleistocene. Some geologists are incensed. "All of a sudden they want to move [the Pleistocene] down 800,000 years," says marine geologist Lucy E. Edwards of the U.S. Geological Survey in Reston, Virginia. "Why? 'Because we want it.' It upsets the stability of the nomenclature without a good scientific reason. Many more marine geologists working in the Pleistocene would be completely discombobulated."

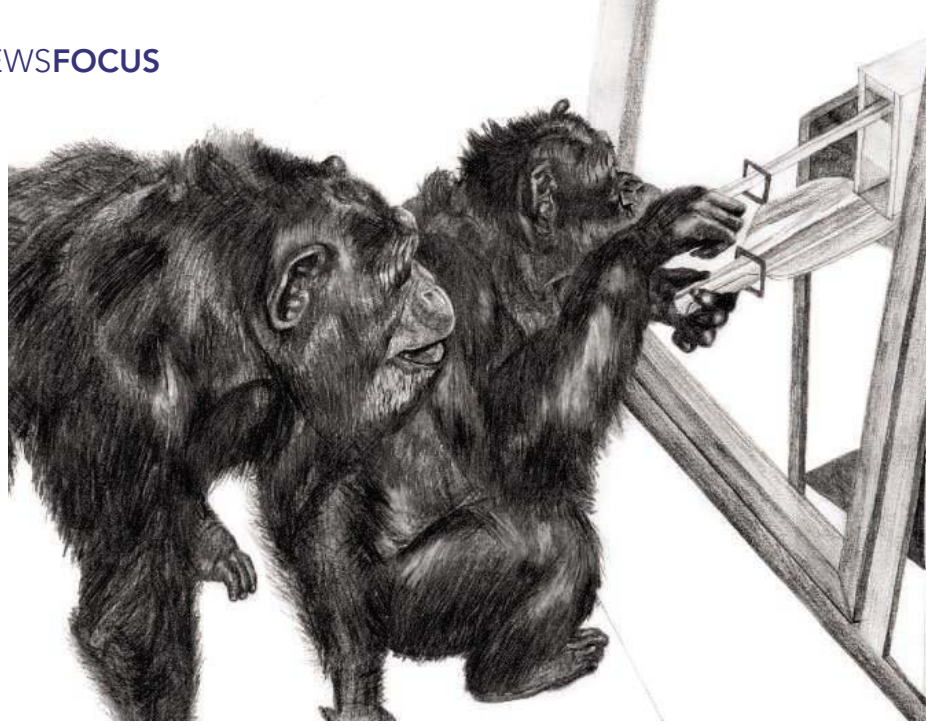
Critics say the revision violates a basic rule: that boundaries on the time scale are not delineated by climate changes such as revved-up ice ages. Exactly when a climate event appears in the geologic record, they point out, can depend on the latitude where the record was laid down. Edwards says quaternarists would take the boundary to be "when the glaciation started where *I* work." Marine geologist Marie-Pierre Aubry of Rutgers University plans to hold firm against the change. "Are we going to give up our principles?" she says. "I don't believe so."

Proponents of the proposal point out that the proposal pegs the Quaternary's lower boundary to an extremely well defined climate event: a sharp swing recorded at the same time at all latitudes in marine-sediment oxygen isotopes. But it still doesn't pass muster with marine geologists. "Climate change is not a criterion for defining units except for quaternarists," Berggren says. "They think climate change at 2.6 million years is the most important thing, [but] climate changes are not unique signals in the record." Similar climate oscillations precede and follow the chosen swing, he notes, and major episodes of glaciation have occurred for hundreds of millions of years. "The rest of the community is going to ignore it," he says.

The arguments will come to a head this August at the 33rd International Geological Congress in Oslo. "We're going to make time for an open forum and discussion," says Peter Bobrowsky of the Geological Survey of Canada in Ottawa, who is secretary general of IUGS. "We hope to resolve the matter of the Quaternary [in Oslo] or agree on how to resolve it." He says he expects a good outcome, if only because IUGS has ruled that nothing will be carved in stone before 2009. Oslo "could be a free-for-all," he says. "It won't be a bloodbath. They *are* academics."

–RICHARD A. KERR

CREDITS (LEFT TO RIGHT): COURTESY OF WILLIAM BERGGREN; COURTESY OF PHILIP GIBBARD



Watch me! The ability of chimps to learn from each other may have been underestimated.

HUMAN EVOLUTION

Why We're Different: Probing the Gap Between Apes and Humans

Researchers at a high-level meeting probe the ancient question of what sets the human brain apart from that of other primates

GÖTTINGEN, GERMANY—We sometimes see apes and monkeys in the movies, but we never see them *at* the movies. Although nonhuman primates can do remarkable things—chimps have rudimentary cultures, and some monkeys have highly complex social systems—none shows the kind of creativity and innovation that are the hallmarks of *Homo sapiens*. Researchers have long puzzled about which human behaviors stem from our primate roots and which are unique to the hominid line.

Beginning in the 1960s, scientists focused on the similarities, as lab and field studies revealed that the cognitive talents of other primates had been underestimated. But during the past decade or so, researchers say, there has been renewed interest in the traits that set us apart. At a recent meeting* here, anthropologist Carel van Schaik of the University of Zurich, Switzerland, emphasized this evolutionary divergence. "Mind the gap!" he said in a keynote talk. "Humans have a huge number of [novel] characteristics." Indeed, participants at the meeting, which was designed to compare and contrast humans and nonhuman primates, demonstrated several of these seemingly unique human behaviors: advanced planning (the conference was months in the making), social organization and cooperation (everyone showed up at the same time and place), and culture and teaching through language.

At the conference, researchers heard evidence that many of these behaviors, such as planning, may have deep evolutionary roots. But some talents, such as cultural innovation, seem unique to our species, and others, including altruism, may represent a novel blend of old and new characteristics. The challenge now, says van Schaik, "is to figure out how one ape among many—humans—could become so radically different."

The waiting game

"Genius," said the 18th century French naturalist Buffon, "is only a great aptitude for patience." To many researchers, our ability to trade immediate gratification for long-term rewards sets us apart from other, more impulsive animals. Without patience, activities from planting crops for later harvest to sending space probes to Mars would be impossible. But a talk at the meeting by behavioral ecologist Jeffrey Stevens of the Max Planck Institute for Human Development in Berlin suggests that patience has evolutionary roots that predate the ape-human split—and that in some situations, humans may be even more impulsive than apes.

Most studies suggest that animals have a low tolerance for delayed gratification. When offered a choice between two food pellets immediately or six pellets later, pigeons will wait only about 3.5 seconds for the larger reward. Rats are only slightly less impulsive in similar tests, and even monkeys seem to live largely in the present: In a 2005 study, Stevens found that the patience of marmosets wore thin after 14 seconds. One notable exception is the scrub jay, which stores food for later use and probably represents a case of parallel evolution, says psychologist Nicola Clayton of the University of Cambridge in the U.K., who led the jay research (*Science*, 23 February 2007, p. 1074).

In new studies, Stevens and his co-workers measured how long our closest relatives, chimpanzees and bonobos, would play the waiting game. The apes were placed in an apparatus designed to give them a choice between two grape halves immediately or six grape halves later. (Trial runs taught the apes that the larger food amounts arrived after a delay.) Bonobos accepted a delay of about 74 seconds, whereas chimpanzees sweated out a full 2 minutes to get the larger reward—although they did a lot of fidgeting and head-scratching while they waited.

The experiment shows that a capacity for delayed gratification was already present in the common ancestor of humans and apes, says Stevens. "The ability to restrain impulsiveness would certainly seem to be a prerequisite for the sort of planning we see in many human activities," agrees primatologist Dorothy Cheney of the University of Pennsylvania.

Stevens also tried to directly compare humans and chimps in a similar experiment. To his surprise, humans (who were eating raisins, M&M candies, or popcorn) caved much more quickly than apes: About 72% of the chimps waited the 2 minutes for a bigger share, whereas only 19% of the humans did so. But given humans' ability to buy groceries for the week, van Schaik suspects that "people did not really take the experiments as seriously as the chimps."

This cricket's on me

Although chimpanzees may be surprisingly patient, they fail miserably at another typically human behavior: lending a spontaneous helping hand to one's neighbor without

* Primate Behavior and Human Universals, Göttingen, Germany, 11–14 December 2007.

CREDIT: AMY WHITEN

expecting anything in return. Such altruism is very common among humans, some of whom even sacrifice their own lives to help others. Yet recent work by anthropologist Joan Silk of the University of California, Los Angeles (UCLA) and Michael Tomasello of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, has shown that chimps, although remarkably cooperative in many ways, do not spontaneously help fellow apes. Other work has found that most nonhuman primate cooperation involves self-interested reciprocal exchanges. Many scientists have concluded that true altruism requires higher cognition, including an ability to read others' mental states, called theory of mind (*Science*, 23 June 2006, p. 1734).

Yet humans may not be the only altruistic primates. A team led by Judith Burkart of the University of Zurich, which included van Schaik, looked for helping behavior in marmosets, who lack advanced cognition but are highly cooperative. One monkey, the donor, was given a choice of pulling a tray with a bowl that contained a juicy cricket or pulling a tray with an empty bowl into an area where another monkey was sometimes present. Only the recipient could get the food, with no payoff for the donor. Nevertheless, the donor pulled the cricket tray an average of 20% more often when a recipient was present than when it was absent, Burkart said at the meeting. Moreover, the marmosets were about equally generous to genetically unrelated monkeys as they were to their kin.

Why do marmosets and humans engage in spontaneous altruism when other primates do not? The answer, Burkart proposed, is that both species, unique among primates, are cooperative breeders: Offspring are cared for not only by parents but also by other adults. Marmoset groups consist of a breeding pair plus an assortment of other helpers, whereas human parents often get help from grandparents, siblings, and friends. Burkart suggests that primate altruism sprang from cooperative breeding. In humans, these altruistic tendencies, combined with more advanced cognition, then nurtured the evolution of theory of mind.

"This is an excellent piece of work," says Silk, although she cautions against drawing sweeping conclusions about the evolution of human altruism from "just two data points," humans and marmosets. Nevertheless, Tomasello says, if the results are valid, they "demonstrate that generosity with food and complex cognitive skills are independent adaptations, which humans may have combined in unique ways."

Cultural ratchet

Researchers agree that cultural innovation is one arena in which humans stand alone. Chimps and other primates do show signs of rudimentary culture, such as different traditions in the use of tools to crack nuts (*Science*, 25 June 1999, p. 2070). But the highly complex cultures produced by human societies are unique to our species. What accounts for this cultural gap?

Some scientists, including Tomasello and UCLA anthropologist Robert Boyd, who both attended the meeting, have argued that other primates are poor at imitating others and learning from them. Humans, in contrast, are such good imitators that they accumulate culture and knowledge over generations, a "ratcheting" effect that bootstraps the slow pace of biological evolution with a powerful dose of cultural evolution.

Beyond the family. Did cooperative breeding help make both marmosets and humans altruistic?

CREDIT: JUDITH BURKART

Yet studies led by psychologist Andrew Whiten of the University of St. Andrews in Fife, U.K., have found that chimps' ability to imitate might be underrated. Some of these experiments have employed a special food dispenser that can be operated both by poking a stick into it and by using the stick to lift a lever. When chimps who had learned one or the other technique from humans were reintroduced to their peers, the other animals quickly learned to follow their example (*Science*, 26 August 2005, p. 1311). But Tomasello suspected that the chimps might be emulating the motion of the dispenser rather than imitating another chimp.

In new work reported at the meeting, Whiten and his co-workers claim to have ruled out that possibility. They tied a length of fishing line to a lever so that they could surreptitiously pull it to deliver a grape. Yet when 12 chimps were exposed to this "ghost" apparatus, none learned to pull the lever themselves. The team concluded that chimps could only learn to use the machine if taught by another chimp or a human—through social learning or imitation.

"A decade ago, people were doubting" that social learning took place in nonhuman primates, says Joanna Bryson, a cognition researcher at the University of Bath, U.K. "Since then, Whiten has … prove[d] beyond a doubt that it occurs."

Whiten said at the meeting that these results suggest that imitation was in place long before cultural ratcheting and imply a somewhat different model for cultural evolution from that of Tomasello and Boyd. The element that kept chimps and possibly early hominids from complex culture might have been a poor ability to innovate, he suggested. For example, early humans made Acheulean hand axes in the same basic form for hundreds of thousands of years.

Van Schaik agrees with this logic: "It might be that apes … fail to produce anything that goes beyond what they already have." And Tomasello now says his earlier views require modification. "[Whiten's results] demonstrate that chimpanzee social learning is more powerful than I previously thought," he says.

Indeed, for some researchers at the meeting, talks such as Whiten's suggested that the evolutionary gap between humans and other primates might not be insurmountable. "We are just primates with a particular combination of traits," says Bryson. "Seeing how all those traits came together and exploded into our current culture is really interesting. It makes you wonder whether it might happen soon for another species, given a chance."

–MICHAEL BALTER

NEUROSCIENCE

Shell Shock Revisited: Solving the Puzzle of Blast Trauma

Even at a distance, explosions may cause lasting damage to the brain. Such findings could have big implications for arming and compensating troops

Working at the Military Hospital in Belgrade during the brutal Balkan war of the 1990s, neurologist Ibolja Cernak encountered a medical enigma. She saw soldier after soldier with memory deficits, dizziness, speech problems, and difficulties with decision-making—but no obvious injury. Cernak recalls one 19-year-old who went to a grocery store and began to weep after he couldn't remember how to get back home. When his mother brought him to the hospital a few days later, Cernak learned what later emerged as a common element in all these cases: The soldier had survived an explosion on the battlefield.

The strange thing was that most of these patients had not suffered a direct injury to the head. And yet, in computed tomography and magnetic resonance imaging scans, Cernak saw signs of internal damage. In some cases, the brain's ventricles—channels that carry cerebrospinal fluid—had become enlarged; and in some, there was evidence of minor bleeding. But when Cernak dug into the medical literature for an explanation, she came up empty. According to the available research, shock waves from an explosion injure mainly air-filled organs such as the lung and the bowel, not the brain.

With a small band of collaborators in Belgrade, China, and Sweden, Cernak undertook animal studies that eventually confirmed that blast waves can cause neuronal damage. The work drew little attention until 2 years ago when hundreds of U.S. and British soldiers began returning from Iraq with symptoms similar to those of Cernak's patients. As roadside explosions became more common, military doctors suspected that these symptoms were the likely result of mild traumatic brain injury (TBI) sustained in blasts. Seeing her observations borne out was as if "a myth had become reality," says Cernak, who is now a researcher at the Applied Physics Laboratory at Johns Hopkins University in Baltimore, Maryland.

How blasts affect the brain has since become an urgent question in military medicine. Last summer, the U.S. Congress gave $150 million to the Department of Defense (DOD) for the first year of research on TBI—both severe injuries that damage the skull and milder ones suspected of causing neurological deficits. The Defense Advanced Research Projects Agency (DARPA) has already launched a $9 million research program aimed specifically at understanding trauma caused by shock waves, heat, and electromagnetic radiation emanating from blasts. Another $14 million a year is going to the Defense and Veterans Brain Injury Center (DVBIC), a DOD-funded agency headquartered in Washington, D.C., for research and outreach on TBI.

This flurry of interest has focused a spotlight on Cernak's research. There is growing consensus that blasts can produce subtle injuries in the brain as suggested by Cernak several years ago. In fact, the Department of Veterans Affairs (VA) proposed a new rule this month acknowledging blast-related TBI as a special neurological condition whose symptoms may have gone undetected in the past. The proposed rule, published in the *Federal Register* on 3 January, would allow for greater disability compensation to victims than is granted currently.

But many researchers are skeptical of Cernak's ideas about how these injuries might occur. Cernak postulates that blast waves ripple through the victim's torso up into the brain through the major blood vessels, leading to neurological effects that can be slow to appear. Although she has evidence from animal experiments to back up that hypothesis, she admits that more research is needed. If the mechanism is confirmed by future studies, Cernak says, it would mean that helmets do not protect the brain against blast injury.

Besides raising questions about the protection of troops currently in combat, Cernak's suggestion that simply being exposed to an explosion might lead to long-lasting brain damage has opened a Pandora's box, particularly for veterans. It implies that some could be suffering from neurological deficits that went undiagnosed or were mistakenly attributed to posttraumatic stress disorder (PTSD). Indeed, since the

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government began putting out information about blast-related TBI, veterans have been trickling in to seek treatment for mental problems that some have lived with for decades. "It may well be that blast injuries follow the pattern of Agent Orange and Gulf War syndrome," says former VA psychiatrist David Trudeau, referring to ill-defined health problems that have lingered for years after battle.

Hidden trauma

If Cernak had been a doctor during World War I, she says, she might well have recognized mild TBI among the thousands of soldiers who suffered from what was simply called "shell shock." But during World War I, many doctors and military commanders viewed shell shock as a transient psychological phenomenon that affected soldiers who, in their opinion, were mentally weak.

Cernak discovered something very different: that soldiers' mental problems seemed to be driven by enduring physical changes in the brain. To test her hypothesis, she conducted a study of 1300 patients who had suffered penetrating wounds to the lower body but not the head. More than half had suffered injuries in a blast; the rest had been wounded by projectiles. Many of the blast victims complained of symptoms such as insomnia, vertigo, and memory deficits, and more than 36% in this group showed irregular patterns of electrical activity in the brain—as measured by electroencephalograms taken within 3 days of the injury—compared to only 12% in the other group. A year later, 30% of blast-injured patients still showed abnormal brain activity compared to 4% of the rest. Cernak says the findings, published in the *Journal of Trauma* in 1999, suggested that the mental problems of blast victims had a biological basis.

Her study wasn't the first to make that point. A year earlier, VA researchers had found that among veterans with PTSD, individuals with a history of blast exposure were much more likely than others to have abnormal brain activity as well as cognitive and behavioral problems. "Our evidence pointed to the possibility that blast injury was a long-lasting injury in combat veterans," says Trudeau, who retired in 2000. He says he was disappointed by the lack of follow-up to the study, published in the August 1998 *Journal of Neuropsychiatry*. "The reception we got was pretty lukewarm," he says.

For decades, Army researchers had been studying the effects of blast waves but with a different focus. They concentrated on how to protect the lungs and bowel because the pressure from an explosion is most likely to shear at the interface of these tissues, where densities differ. DOD was so confident that advanced body armor was protecting troops against lung and bowel injuries that it closed down this research program in 2003. "We thought, why spend more money on this when we've fixed the problem?" says Geoffrey Ling, a neurologist and a program manager at DARPA.

Then the bad news arrived. As blast survivors from Iraq were air-lifted to hospitals, U.S. Army doctors, including Ling, who was deployed in Iraq in late 2004, began to see patients whose brains had swelled markedly within hours of being close to a blast. Some had clear head injuries but many did not. Even in cases involving visible wounds, the extent of swelling was often much greater than expected, leading neurosurgeons to wonder whether blast waves had played a role in addition to penetrating shrapnel. Ling says the patterns of vascular enlargement seen across a range of patients showed a continuum of brain injury, suggesting that there could be milder versions that were less obvious.

CREDIT: ED WHITMAN/JOHNS HOPKINS APPLIED PHYSICS LABORATORY

"What's happening in blast injury is that these inner structures [of the brain] are being affected."

—IBOLJA CERNAK, JOHNS HOPKINS UNIVERSITY

That suspicion has grown stronger with hundreds of soldiers returning from the war zone complaining of a common cluster of cognitive and behavioral problems. Army doctors say they have encountered many patients who are unable to perform simple addition and subtraction, read more than one sentence at a stretch, or recall simple things like what they had for lunch. "The majority are individuals who lost consciousness or were dazed after a blast but did not sustain overt head injuries," says Ronald Riechers, a neurologist at Walter Reed Army Medical Center in Washington, D.C. "Within a short time frame, they develop headaches and notice that their reaction time and concentration are not the same as before." Based on these evaluations, DVBIC estimates that 10% to 20% of all soldiers on duty in Iraq and Afghanistan have suffered some type of TBI.

Ling says the TBI numbers prompted DOD to restart its research on blast injury, this time with a focus on the brain. DARPA is funding two main projects as part of the first basic science effort on the topic. One will study the mechanical and cellular effects of blast waves in an animal model. Another will look at the consequences of repeated exposures to low-intensity explosions among military breachers, whose job is to blast holes into buildings using shoulder-launched weapons. "Once you know for certain what in a blast is really hurting the brain and how, you can use that to develop therapies and prevention strategies," says Ling.

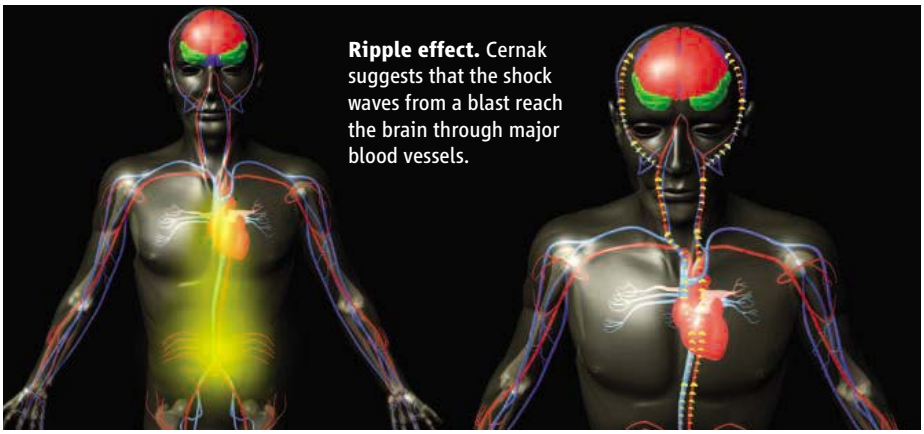
A tsunami in the brain

Although it is becoming accepted that blast waves can cause TBI, Cernak's theory about how the damage occurs is controversial, and it has implications for how best to protect troops. She hypothesizes that when blast waves strike the body, they transfer kinetic energy and cause pressure in the main blood vessels to oscillate rapidly. A pulse travels up through the neck into the brain, damaging axonal fibers and neurons in the hippocampus, brainstem, and other structures close to cerebral vessels. The shock can also injure cells farther out in the cortical regions.

That mechanism is entirely different from the more widely studied effects of acceleration or deceleration in a car crash. Researchers know that a crash impact can shake the brain so violently that axonal fibers are torn. Some say victims of explosions could be experiencing a similar whiplashing, in contrast to Cernak's view—which would mean that helmets designed to dampen that effect could help.

"I am very skeptical that kinetic energy could be transferred through the vascular system," says J. Clay Goodman, a neuropathologist at Baylor College of Medicine in Houston, Texas. "It is much more reasonable to consider the blast effects directly on the cranial vault and the brain."

Cernak says her findings show the vascular route to be more plausible. In experiments that exposed rats and rabbits to a simulated blast wave in a shock tube—a cylinder through which an air pulse is transmitted at high velocity—Cernak and her colleagues found that immobilizing the animal's head with steel plates to prevent whiplash effects did not protect against hippocampal cell damage, as they reported in the *Journal of Trauma* in 2001. Cernak says the vascular-transmission theory could explain the unique combination of symptoms in blast-induced TBI, as well as why neurological symptoms are seen in soldiers wearing helmets. For example, memory deficits hint at damage to the hippocampus, whereas problems in orientation reflect injuries to the cerebellum. "What's happening in blast injury is that these inner structures are being affected," Cernak says, in contrast to TBIs in traffic accidents and contact sports, where the cortex bears most of the brunt.



Ripple effect. Cernak suggests that the shock waves from a blast reach the brain through major blood vessels.

Cernak presented unpublished results last month at the Blast Injury Conference in Tampa, Florida, showing that exposure to blast waves can trigger neurodegeneration in rat brains, fragmenting the walls of neurons in the hippocampus and other regions. Similar findings have been published by Annette Säljö, a researcher at the University of Göteborg in Sweden and a collaborator of Cernak's. Säljö and her colleagues reported in the *Journal of Neurotrauma* in August 2000 that rats exposed to blasts showed a buildup of neurofilament proteins in the cortex and the hippocampus during the week following the injury. This suggests that the damage can worsen over time, like a "slow cooking under the surface," says Cernak: "One could think of it as a horribly accelerated aging of the brain."

If blast waves indeed cause injury by vascular transmission, new types of body armor may be needed. "We would need to develop materials that completely absorb or reflect the full range of blast-wave frequencies generated by an explosion," says Cernak, adding that current body armor only shields against some of a blast's kinetic energy.

Cernak has done pioneering work, says John Povlishock, a neuroanatomist at Virginia Commonwealth University in Richmond, adding that she may be right that a "rapid rise and fall in venous pressure" is what stamps the blast's signature on the brain. But more studies are needed to validate her ideas and translate the animal results into humans: "This is a topic with great economic, military, and social implications," he says, "and as of now, the literature is extremely limited."

Needed: A gold standard

As blast casualties from Iraq have mounted, the U.S. military has stepped up efforts to detect TBI among troops. In July 2006, the Army Surgeon General asked all unit commanders in Iraq to request TBI screening for soldiers displaying "poor marksmanship, delayed reaction times, decreased ability to concentrate, and inappropriate behavior." Troops who have been in a blast are evaluated by field medics using a short questionnaire that asks, among other things, if the person lost consciousness and had trouble remembering things from just before the explosion. Depending on the severity of the symptoms, they are asked to take a day off or see a neuropsychologist.

Some veterans groups believe a more aggressive screening policy is needed, especially because the symptoms of blast injury might not show up until later and because subtle injuries might not show up in standard brain scans. The ideal option, some say, would be to use a biomarker: "We'd like to be able to do a blood test to determine the injury," says Colonel Robert Labutta, a neurologist at the health affairs office at DOD. But until the science of blast injury is established, officials say, it does not make sense to bring home every soldier who has been in the vicinity of an explosion.

The costs of treating TBI victims from Iraq and Afghanistan could be astronomical. At last count, nearly 25,000 soldiers had been diagnosed with TBI. One estimate of the financial burden, calculated by Harvard researchers, puts the number at $14 billion over the next 20 years. But officials seem determined not to miss any cases among troops coming home: In April, VA mandated TBI screening for all Iraq and Afghanistan veterans who come to VA hospitals for any services, even if it's a dental exam.

The spotlight on mild TBI has drawn the attention of older combat veterans who were exposed to blasts but were never treated for neurological symptoms. Many were diagnosed with PTSD; some of the symptoms—such as depression, irritability, and attention deficit—overlap with those of mild TBI. These cases, some reaching back to the Vietnam War, could have significant legal and financial implications, says Edward Kim, a psychiatrist with Bristol-Myers Squibb in Plainsboro, New Jersey, and author of a recent report from the American Neuropsychiatric Association on the mental health effects of TBI. "I question whether DOD and the VA really want to open this can of worms," he says. For example, a veteran with Alzheimer's disease could make a claim pointing to research showing that TBI increases the risk of developing Alzheimer's disease.

Cernak says she has been receiving e-mails and phone calls from veterans thanking her for her research and seeking more information. Last month, she got a call from a 47-year-old woman who had served in the first Gulf War. The woman had been a teacher before she went to the combat zone, where she was exposed to repeated blasts. After she returned home, she had to stop teaching because she could not remember any facts. The story reminded Cernak why she had begun studying this obscure field 2 decades ago. "Soldiers anywhere are one of the most vulnerable populations in the world," she says. "It is a moral obligation to help them."

–YUDHIJIT BHATTACHARJEE

CREDIT: IBOLJA CERNAK AND JACOB ELBAZ/JOHNS HOPKINS UNIVERSITY APPLIED PHYSICS LABORATORY

LETTERS

edited by Jennifer Sills

Antarctica Invaded

Not so remote. Tourism is one factor affecting Antarctica's previously isolated ecosystem.

THE PERSPECTIVE "ANTARCTIC BIODIVERSITY" (P. CONVEY and M. I. Stevens, 28 September 2007, p. 1877) highlights endemic fauna and flora on the south polar continent that have persisted through glacial cycles and remained geographically isolated for millions of years. However, this ancient biota is no longer isolated. Despite being surrounded by a vast ocean, Antarctica's isolation has diminished rapidly for a variety of reasons: a burgeoning tourist industry that produces tens of thousands of visitors each year; scientific exploration; increased accessibility by air and by sea; and global warming, which is removing physiological barriers to colonization by species that previously could not survive the inhospitable climate (*1*, *2*).

Human activity in Antarctica is taking its toll. In one alarming example, poultry viruses and *Salmonella* have been found in penguins (*3*). This discovery garnered media attention, but invasions by many other organisms have occurred with less fanfare. Nearly 200 alien species of fungi, terrestrial plants, invertebrates, and vertebrates have colonized the Antarctic continent and its surrounding islands within just the past two centuries (*1*), an astonishing rate for this once intensely remote region. On Gough Island, for example, the modern rate of invasion may be as much as 20,000 times higher than the prehistoric rate (*4*). Although their effects have been poorly studied to date, alien species have already reduced populations of native plants, invertebrates, and seabirds (*5*–*7*), and they have had direct and indirect effects on ecosystem processes (*1*, *8*). The dramatic effects that alien species have had in insular endemically rich regions elsewhere (*9*–*11*) warn that they could play a major role in reshaping Antarctica's diversity.

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A Closer Look at the IPCC Report

IN THEIR POLICY FORUM ("THE LIMITS OF consensus," 14 September 2007, p. 1505), M. Oppenheimer *et al*. make several misleading statements. They suggest that a premature drive for consensus led Working Group I to understate the risk of large future sea-level rise in the Intergovernmental Panel on Climate Change (IPCC) Fourth Assessment Report (WGI-AR4). They assert that the "Summary for Policymakers" (SPM) of the WGI-AR4 did not properly consider increasing contributions from rapid dynamical changes in the ice sheets of Greenland and West Antarctica (WAIS). However, in quoting the SPM discussion of sea-level rise, they ignore its explicit statements on the subject, such as "dynamical processes related to ice flow not included in current models but suggested by recent observations could increase the vulnerability of the ice sheets to warming, increasing future sea level rise"; the model projections "[do not] include the full effect of ice sheet flow because a basis in published literature is lacking"; and, crucially, "larger values cannot be excluded, but understanding of these effects is too limited to assess their likelihood or provide a best estimate or an upper bound for sea level rise" (*1*).

We agree with Oppenheimer *et al*. that paleoclimatic observations should be considered in assessing possible long-term future sea-level rise and polar ice sheet changes, but dispute their inference that the SPM omitted the available information. The SPM explicitly noted that "global average sea level in the last interglacial period (about 125,000 years ago) was likely 4 to 6 m higher than during the 20th century, mainly due to the retreat of polar ice" from Greenland and possibly Antarctica as well. The SPM refers to the whole of Antarctica because of the possibility of differing behavior for the East Antarctic Ice Sheet (for which there is currently some evidence for mass gain, as opposed to mass loss of WAIS), in order to communicate with policymakers whose interest lies in understanding the total contribution to sea-level rise.

Oppenheimer *et al*. offer a number of suggestions for handling uncertainty, but they do not address the fact that quantitative model projections of ice-sheet dynamical changes cannot yet be made because of the

CREDIT: FRANS LANTING/CORBIS

inadequacy of current scientific knowledge. Observations do not presently offer a clear way to progress past these model limitations, in part because of discrepancies among published studies: Whereas some suggest that currently observed flows in outlet glaciers may be transient and thus have limited implications for long-term sea-level rise, others suggest the opposite.

IPCC assesses the literature; it does not conduct new research. In our view, providing numerical estimates of potential sea-level rise due to processes not yet quantified in the literature (whether by expert elicitation, as suggested by Oppenheimer *et al*., or by another process) would lead to inappropriate "anchoring around numerical values" of exactly the type that Oppenheimer *et al*. warn against. Far from minimizing structural uncertainties, or driving for a "premature consensus," as Oppenheimer *et al*. suggest, the SPM text of the WGI-AR4 appropriately does the exact opposite by explicitly stating that "understanding of these processes is limited and there is no consensus on their magnitude."

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Response

We disagree with Solomon *et al*. that our Policy Forum was misleading. We correctly noted that model-based numerical ranges for 21st-century sea-level rise presented in the WGI SPM (Table SPM-3) did not account for the uncertainty resulting from potential increases in the rapid dynamical response of ice sheets. Solomon *et al*. challenge this assertion by pointing instead to qualitative statements in the SPM, implying that the latter provide a satisfactory accounting of uncertainty. But the distinction between numerical values highlighted in a prominent table and narrative qualifications of such numbers is critically important. Numbers are powerful, grabbing the readers' attention, whereas qualifications are often ignored. For example, the tabular values, indicating a maximum sea-level rise of 59 cm during the 21st century, are cited frequently in the public discussion absent any qualification.

We did not imply, as Solomon *et al*. argue, that the WGI SPM omitted information from paleoclimate studies in evaluating uncertainty in sea-level rise beyond the 21st century. We suggested that it gave too much credence to ice-sheet models compared with other sources of information. For example, in reporting only a model-based estimate for the time scale of a long-term contribution (from Greenland), the WGI SPM gives short shrift to the implications of observations of fast responses in both Greenland and WAIS, narrative qualifications to the contrary notwithstanding. Such an approach understates the range of opinion in the relevant expert community on the potential magnitude and rate of the ice-sheet contribution as indicated by studies reviewed during AR4 (*1*). Further perspective on this question is provided by the AR4 Synthesis Report (*2*).

Finally, contrary to Solomon *et al*.'s assertion, our suggestions for improving the treatment of uncertainty were made specifically with the shortcomings of ice-sheet modeling in mind. It makes little sense to highlight model-based projections of sea-level rise when models that are supposed to account for the ice-sheet component have failed the test against reality. Other approaches provide important additional perspectives. For example, the fact that two independent semi-empirical analyses estimating uncertainties in future sea-level rise have been published recently (*3*, *4*) suggests that observation-based methods yield important insights where models are deficient.

We do not propose that IPCC "conduct new research." Rather, we argue that it take full advantage of what has already been produced. IPCC also has the flexibility to fill gaps in modeling and analysis where the completeness of assessment calls for it, and has done so many times. In anticipation of a Fifth Assessment, and realizing that ice-sheet models may not improve rapidly, IPCC should encourage the development of a more comprehensive approach to uncertainty. As it has done for other arenas, such as emissions scenarios or abrupt climate change, IPCC could spur research into empirical approaches, formalized expert elicitation, and comprehensive analysis of paleo-ice extent and sea level, each carried out with a specific view toward informing quantitative judgments on the range of future sea level. Holding workshops on this problem over the next few years would fit neatly into IPCC tradition.

Three of us are authors of AR4, well aware of the difficulty of assessment. A premise of our Policy Forum is that IPCC has done a superb job of establishing the scientific consensus. But in a high-stakes problem like global warming, governments need to calibrate policy to the full range of plausible outcomes, for sea-level rise and for all other key uncertainties.

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CORRECTIONS AND CLARIFICATIONS

News Focus: "Gunning for the Ivy League," by H. Xin and D. Normile (11 January, p. 148). In the chart titled "Higher Education in China," the unit label for the *y* axis should have been thousands, not millions.

Special Issue on The Cosmic Web: News: "Untangling the celestial strings," by A. Cho (4 January, p. 47). The first Pan-STARRS telescope is located at Haleakala Observatories, Maui, not on Mauna Kea as the article stated.

Policy Forum: "Implementation science" by T. Madon *et al*. (14 December 2007, p. 1728). The authors' affiliation is The John E. Fogarty International Center at NIH; the division name is incorrect and should have been removed.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

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HISTORY OF SCIENCE

The Many Sides of Science

Manfred D. Laubichler

Vienna in the Age of Uncertainty
Science, Liberalism, and Private Life
by Deborah R. Coen
University of Chicago Press, Chicago, 2007. 392 pp. $45, £28.50. ISBN 9780226111728.

Ludwig Wittgenstein, arguably Vienna's most famous philosopher, introduced the idea that "language games" represent specific ways of life and thought. Wittgenstein's debt to the rich and often contradictory intellectual and artistic environment of his native city is by now well known, and cultural historians have described the unique symbiosis of philosophy, science, art, and politics in imperial Vienna (*1*–*3*). Deborah Coen's *Vienna in the Age of Uncertainty* is an important contribution to this rich literature, one that will especially interest those fascinated by the varied interactions among science, society, and culture.

Coen, a historian of science at Barnard College, presents the biography of a scientific dynasty, the prolific Exner family. It includes the chief architect of Austria's mid-19th-century education reforms (the philosopher Franz); physicists Franz Serafin and Karl, physiologist Sigmund, and legal scholar Adolph (all second generation); meteorologist Felix and Nobel laureate ethologist Karl von Frisch (third generation); several physicians and jurists; and, especially among the women, talented artists and social activists. Both Adolph and Franz Serafin served as rector of the University of Vienna, and several Exners were members of the Austrian Academy of Sciences. Thus in terms of their scientific prominence, the Exner dynasty is on par with the Darwin and Huxley families in Britain. But unlike their well-studied British counterparts, the Exners have been rather neglected.

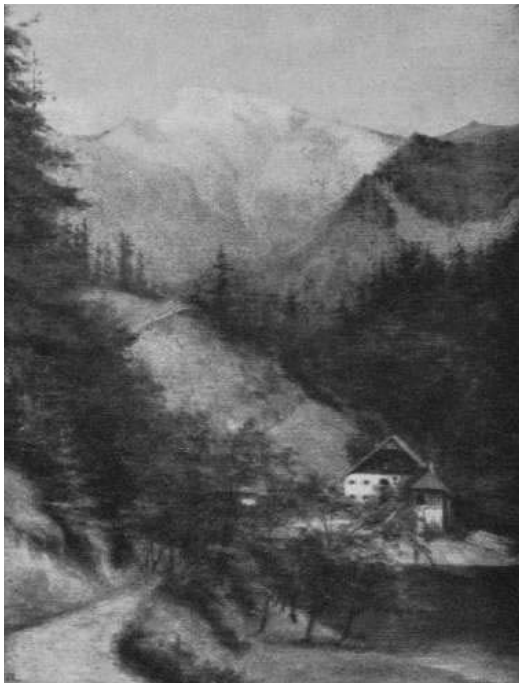
To be sure, their individual discoveries and accomplishments—educational philosophy (Franz), contributions to color perception and the physiology of vision (Sigmund), statistical physics (Franz Serafin), meteorology and alpine climate (Felix), and the "language of the bees" (von Frisch)—are well established. What had been missing was recognition of the intimate connections among these diverse achievements. And it is in this context that Coen's study introduces us to the ideals of the scientific way of life as practiced by three generations of Exners. Foremost among them was the ultimate value of *Vielseitigkeit* (many-sidedness).

Many-sidedness applied to all aspects of the Exners' life and work. It was a cultural value they shared with their peers, the educated liberals of Austria's upper bourgeoisie. These *Bildungsbürger* emphasized the importance of lifelong education through scholarship and the arts and advocated the gradual formation of (as one philosophy textbook that was part of Franz's education reforms put it) an "ethical character through the systematization of empirical rules."

Like many members of their class, the Exners spent summers in the countryside, away from the busyness of Imperial Vienna. The ever-growing family congregated at Brunnwinkl, a compound purchased in 1882 by Marie von Frisch (née Exner), on the Wolfgangsee in the Salzkammergut region (a popular destination for summer vacationers, including Emperor Franz Joseph). Here the children explored the woods and the lake while also participating in the artistic and intellectual pursuits of their parents, which included painting, music, literature, and (of course) scientific and philosophical discussions. This environment was greatly enriched by distinguished guests and visitors, such as writers Gottfried Keller and Marie von Ebner-Eschenbach and surgeon Theodor Billroth. The meadows of Brunnwinkl were also the decades-long laboratory for Karl von Frisch's experiments with bees. Coen details the importance of this country retreat for the development and refinement of the Exners' scientific and cultural way of life, thus adding to the recent emphasis on the "power of place" in the history of science (*4*).

Another major focus of Coen's study is the scientific and cultural significance of uncertainty. The uncertainty linked to the increasing cultural and political complexity of fin-de-siècle Vienna has been blamed for the emergence of radical movements in politics and art that ultimately undermined the carefully balanced liberal consensus and paved the way for both relativism and fascism. Coen puts this simplistic view to rest. She carefully reconstructs how "uncertainty" and the associated methodology of statistical reasoning became the foundation for many of the scientific advances of the Exner dynasty. Here too, distinctions between scientific methodology and a way of life were blurred. For the Exners, accepting the complexity of the world and the many different possibilities it entails required the application of a careful method (in both their life and science) to arrive at reasoned conclusions based on incomplete evidence. These skills would have been honed from early childhood on, and rather than an abstract syllogism, the very real figures of the hunter and the farmer (whom the Exner children encountered during their stays at Brunnwinkl) served as a methodological guide. This reliance on practical knowledge is reminiscent of Darwin's debt to pigeon fanciers and breeders of animals and plants. As in Darwin's approach, the Exners' methodological repertoire highlighted the importance of variation, errors, and fluctuations in experimental science, and this emphasis led them to new discoveries in a variety of different disciplines. But, insofar as uncertainty is also a reflection of the many possible sides of nature and culture (*5*, *6*), the Exners' focus on capturing rather than taming chance is yet another expression of their core values.

The many-sided life of the Exners, presented so skillfully by Coen, serves



Salzkammergut scene. This watercolor by Marie Exner von Frisch served as the frontispiece to a reminiscence (*7*) by her son Hans, a law professor and opponent of the Dollfuss regime.

CREDIT: (7)/COURTESY DEBORAH COEN

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to remind us all about the responsibilities of scientists to not focus only on a specific problem and to search for connections beyond the limits of a single discipline. The scientific ethos, which has helped in the past to establish an open and liberal society based on free inquiry and exploration, is once again called upon to defend these values. Therein lies the ethical dimension of a scientific way of life. The satirist Karl Kraus once called Vienna the "Doomsday Laboratory," and the city's 20th-century history shows how fragile the Exners' vision of a liberal humanism actually was. However, as Franz Serafin Exner noted, only through the dedicated efforts of us all will we be able to maintain the highly improbable state of cultural, scientific, and individual diversity.

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NEUROSCIENCE

Steal Away, Music

Jessica Phillips-Silver

Music "steals" us. Far from a passive fancy that lies ready to be called on for the pleasure of our ears and minds, music acts on us. Like the song of the sirens, it seduces us, capturing the mind and body and holding them in its reins. Music has a will of its own when it sneaks up on us with familiar—even unwanted—tunes, "brainworms" that we cannot shake. It taps into memories and emotions so deep-seated that they lie well below awareness in Alzheimer's disease until music brings them to the surface. A Parkinson's patient, unable to will himself to move, relies on music's rhythm and moves. *Musicophilia* is not only another example of best-selling author Oliver Sacks's repertoire of fascinating neurological anecdotes and skillful storytelling but also a poignant collection of evidence that music has a powerful influence on the human brain.

Stories of bizarre and wonderfully human experiences of music float somewhere between the mystical and the medical. The tale of a sudden gift for the piano delivered by a lightning bolt dazzles us, and stories of musical hallucinations and rhythm-induced seizures of the temporal lobes haunt us. We suspend our sensory intuitions to imagine our senses blending like watercolors when a minor third "tastes salty" or the key of D major "looks clear green" in music synesthesias. The chapter titles alone titillate the curiosity, from "Accidental Davening" to "Papa Blows His Nose in G."

Sacks (a professor of clinical neurology at Columbia University) is most at home telling stories of people afflicted by brain damage and deterioration, an inclination revealed by his sensitivity to the unpredictable range of neurological events that carry each patient on a unique mental and emotional journey. Sacks relates his patients' stories with honest insight and a delicate reverence. Moments of humor surprise us, as in the story of the charming Louis, an elderly gentleman with frontotemporal dementia whose loss of inhibition leads him to sing incessantly while chasing after a plate of cookies like an unabashed child.

Gently, we are moved from the funny to the devastating with Clive, a severe amnesic for whom life does not exist beyond the span of several agonizing seconds, except when conducting music or playing the organ. Clive exists only in the present and only through music. When the music stops, so does existence, and he returns to an "abyss" of nonbeing. And we scientists ask, is music adaptive?

Sacks's golden nugget in *Musicophilia* is his insightful description of the ways in which certain brain functions that are normally suppressed get released through damage to others. Damage to the dominant hemisphere, for example, can result in a disinhibition of perceptual abilities associated with the nondominant hemisphere. Thus, through disease or mere aging, individuals, even those who were once artistically or musically naïve, can gain access to perceptual and creative powers. Deafness can lead to musical hallucinations, blindness can lead to music synesthesia, and the disinhibition that occurs in frontotemporal degeneration can lead to sudden, excessive musicality. A shift to right-hemisphere dominance resulting from a lack of normal suppression by the left temporal lobe might contribute to the disproportionate musical abilities in savants and people with Williams syndrome.

Henry Ossawa Tanner's *The Banjo Lesson* (1893).

Neuroscience is delving deep into the brain's musical networks: from the subcortical and cortical structures of musical emotion, to the integration of auditory and motor areas in rhythm; the effects of music training and mental imagery on plasticity, to the role of body maps in musician's dystonia; the asymmetry of the planum temporale in absolute pitch, to the genetic basis of amusia. The field of music neuroscience is young, however, and Sacks's essays are equally nourished by the poetic philosophies of Nietzsche, Eco, and Schopenhauer and the music of Chopin, Chico Marx, and the Grateful Dead. Some mysteries of our creative impulse—the paradoxical way that sad music gives us pleasure, the unique force with which rhythmic music brings a dancing crowd to ecstasy—might just transcend the limits of reason. "The power of music," says Sacks, "whether joyous or cathartic, must steal on one unawares."

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Musicophilia
Tales of Music and the Brain
by Oliver Sacks
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ASSESSMENT

Application of Bloom's Taxonomy Debunks the "MCAT Myth"

Analyses of questions that evaluate critical thinking, from college placement and medical school admission examinations, suggest improvements to college teaching methods.

Alex Y. Zheng,[1] Janessa K. Lawhorn,[1] Thomas Lumley,[2] Scott Freeman[1]*

Biology education and medical education are under scrutiny. The essence of the critique is that introductory biology courses for undergraduates and basic science courses in medical schools overemphasize "factual minutiae" [(*1*), p. 1343] over the things that working biologists and physicians claim students actually need to master—specifically, critical thinking and professional skills (*2*–*4*). The Medical College Admission Test (MCAT) has been accused of hindering efforts to introduce more critical thinking into introductory biology courses (*3*), and the Advanced Placement (AP) Biology course has come under fire for stressing rote memorization (*5*, *6*). Are these criticisms valid? If so, why is there a disjunction between what future biologists and physicians need to know and what they are taught?

To test the hypothesis that some biology-related exams emphasize factual recall, we used Bloom's taxonomy (*7*–*9*) to quantify the level of learning that students are asked to demonstrate on a sample of course exams and standardized tests. Our approach was inspired by literature that uses Bloom's taxonomy to evaluate test questions and student learning (*9*). The taxonomy identifies six levels of understanding. The first four levels (knowledge, comprehension, application, and analysis) are hierarchical, meaning that a student must know and understand a topic in order to apply it to a new situation or analyze it. Only levels 3 through 6 (application, analysis, synthesis, and evaluation) are considered higher-order thinking (*10*, *11*).

The exams we analyzed came from five sources: AP Biology, introductory biology courses for undergraduate majors from three universities in our region, the biology section of the MCAT, the biology Graduate Record Examination (GRE), and five first-year medical school courses from an institution with a traditional curriculum.

Three experts in biology education assessed 586 questions drawn at random from these five sources and used Bloom's taxonomy to assign a Bloom's rating of 1 to 6 to each question (see chart, p. 415). The ratings were done blind, and inter-rater agreement was high (*11*). Before comparing ratings, we weighted them to reflect their point value relative to the other questions sampled from the same exam (*11*). Using the weighted ratings, we compared the proportion of higher-order questions among exam sources and the mean ratings among exam sources using *F* tests based on linear regression (see table, above). Significance levels for pairwise tests were based on Hommel's correction for multiple comparisons.

	n	Weighted proportion of higher-order questions	Unweighted ratings	Weighted ratings
AP Biology	157	0.36 ± 0.06	1.97 ± 0.07	2.35 ± 0.12
Undergraduate	111	0.51 ± 0.07	2.24 ± 0.09	2.43 ± 0.14
GRE	108	0.35 ± 0.05	2.32 ± 0.09	2.32 ± 0.10
MCAT	109	0.45 ± 0.05	2.55 ± 0.09	2.57 ± 0.09
Medical School	101	0.21 ± 0.04	1.97 ± 0.09	1.93 ± 0.08

Representations of higher-order questions. Bloom's ratings from five types of exams (means ± SEM). GRE and MCAT all had only multiple choice (MC) questions; Medical School had only two non-MC questions.

Debunking the "MCAT Myth"

The strongest pattern in our data is the strength of the MCAT exam, which is a good predictor of success in medical school (*12*, *13*). The MCAT has a greater proportion of questions that demand higher-order thinking than our sample of first-year medical school courses ($P = 0.002$); on average, its questions also have a higher average-weighted rating ($P < 0.0001$). These results provide quantitative support for opinions that at least some traditional first-year medical courses are too low-level (*1*, *4*) and, instead, support instructional models that emphasize clinically oriented problem-based learning or case-based learning in the first and second year of medical school [e.g. (*14*)].

When the MCAT is compared with AP Biology or the undergraduate exams in our sample, there is no significant difference in average-weighted Bloom's rating or the proportion of higher-order questions. This is noteworthy because the MCAT is strictly multiple choice, whereas the AP exam and several of the undergraduate exams include essay and short-answer questions. Questions that demand written answers have a much higher average-weighted Bloom's rating [AP exam, $P = 0.003$, and the undergraduate exams in our sample, $P = 0.0002$]. When only multiple-choice questions are included in the analysis, the MCAT and GRE exams have weighted Bloom's ratings that are significantly higher, on average, than the other three sources of exams (table S1 in supporting online material) (*11*).

The MCAT also has the lowest percentage of knowledge-level questions (see chart, p. 415) and the highest average raw question rating of any of our five exam sources (see table, above). These data belie the perception that the MCAT is based heavily on content knowledge and that biology courses must therefore focus more on facts than on skills such as teamwork and the analysis of quantitative evidence (*15*).

Taken together, these observations suggest that the biology portion of the MCAT fulfills its stated goal of assessing problem-solving ability and critical thinking, in addition to mastery of basic biology concepts (*16*).

Should the AP Biology Course and Undergraduate Biology Courses Be Reformed?

We found no significant differences in the proportion of higher-level questions or weighted mean Bloom's ratings in AP biology exams versus the undergraduate exams in our sample. This is surprising, given the extent of criticism that the AP Biology course has received and the College Board's current effort to reform the course with the goal of emphasizing higher-order thinking.

Two observations are relevant here. First, an *F* test confirms significant hetero-

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geneity among the three undergraduate institutions in our sample in terms of proportion of higher-level questions ($P = 0.03$) (*11*). Thus, even our small sample indicates that some undergraduates are being challenged with a greater proportion of higher-order questions in their introductory courses than others. This result suggests that some undergraduate courses need to be reformed to emphasize higher-order thinking skills. Second, the AP Biology exam we analyzed contained 120 lower-level multiple-choice questions worth 60% of the total score and four higher-level essay questions worth 40% of the total score. These exams tested a low-level understanding of a wide array of topics but a higher-order understanding of just four. Thus, criticism (*5*, *6*) of the AP Biology as low-level may be valid, even though the four essay questions are weighted heavily enough to preclude statistically significant differences with the undergraduate exams in our sample.

In addition, the College Board currently validates its exams by having college students take AP exams (*17*). Because of the AP Biology exam's unusual structure, AP coursework should instead be validated by having students from AP courses take college exams.

Disjunction Between Goals and Practice

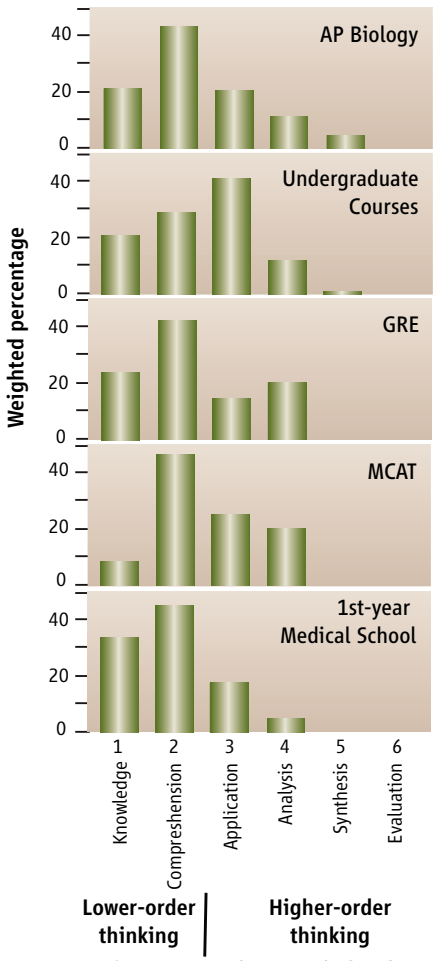
Is there is a conflict between what undergraduates are being taught and what professional biologists and practicing physicians think students need to master? According to our data, this disjunction may be present in biology courses that assess students using only multiple-choice questions and in some traditional medical school curricula. Part of the solution may lie in dispelling the MCAT myth—"freeing" introductory biology instructors to assess at a higher level by convincing them that the MCAT tests more than factual recall. Faculty could also be reassured that because of the hierarchical nature of levels 1 through 4 of Bloom's taxonomy, content isn't "lost" when exams focus on applying and analyzing knowledge and concepts.

Another part of the answer is more practical. It is much more difficult to write multiple-choice questions at the application and analysis levels of Bloom's taxonomy than at the knowledge or comprehension levels (*18*). Experienced practitioners estimate that writing one "good" multiple-choice question takes an hour (*19*). In addition, students perform better on questions that test factual recall than on questions that test their ability to explain or apply concepts (*20*). Writing and taking exam questions that test memorization is much faster and easier—for both student and teacher—than writing and taking exam questions that test higher-order thinking. Our data suggest that there is an urgent need for instructors to create and share multiple-choice questions that test at higher levels of Bloom's taxonomy. The higher orders of thinking are not restricted to essay questions—the MCAT and GRE show that multiple-choice questions can be constructed to test these higher orders of Bloom's taxonomy.

Using Bloom's Taxonomy as a Tool

The general goal of this study was to explore how researchers might use Bloom's taxonomy to quantify and compare levels of assessment from different exams. Because our sample of undergraduate biology courses or first-year medical school courses is small, further analysis should be done for a larger sample of schools, including medical schools with first-year courses that stress clinical application in a problem-based or case-based learning framework.

Because the AP, GRE, and MCAT exams are nationally standardized, however, our assessment of the biology questions on these exams should be robust. It would be interesting to compare the results reported here with analyses of exams from other AP courses in math and science, the Biochemistry GRE, Dental Admission Test, Nursing Entrance Exam, and Pharmacy College Admission Test. Bloom's taxonomy offers a tool for assessing the level of instruction in individual classrooms, monitoring curriculum changes, and making interinstitutional comparisons.



Frequency of exam questions at six levels on Bloom's taxonomy of learning. Proportion of exam questions, weighted to reflect their relative point value, characterized by the six levels of Bloom's taxonomy (*11*).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/319/5862/414/DC1

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GENOMICS

Lining Up to Avoid Bias

Algorithms that align DNA sequences can introduce bias and uncertainty into evolutionary analyses.

Antonis Rokas

Darwin relied on fossils, morphology, and geographical distribution to glean important clues about the history of life. Today, natural historians can study organisms' history of change and adaptation by probing the DNA record. Whether to elucidate evolutionary relationships of genes and species or spot the amino acid changes driven by selection, we need to be able to generate accurate alignments of DNA sequences. On page 473 of this issue, Wong *et al*. (*1*) provide some important caveats on how this can go awry and how to avoid alignment bias.

Sequence alignment is how we identify the similarities in a set of sequences derived from a common ancestor. For very similar genes or proteins we can do this manually, but the alignment of more divergent sequences that have been peppered not only with substitutions, but also with insertions and deletions (collectively known as indels), is particularly challenging. The uncertainty in identifying the precise number and length of indels as well as their exact placement (*2*) creates a multitude of potential ways of aligning distantly related sequences, a computational problem that has given rise to a cadre of alignment-generation programs, each based on a different optimization algorithm (*3*).

For years, the standard protocol has been to pick a favorite algorithm to optimize the alignment it generates. This approach is fast and easy, but it is like being forced to always settle on vanilla ice cream for dessert; doing so can taint one's opinion about ice cream. Similarly, sticking to the use of a single alignment from a single algorithm can bias the estimation of phylogenies (*4*) or of other evolutionary parameters pivotal to our understanding of the DNA record. Until now, the extent and potential significance of this bias introduced by alignment was unknown. Wong and colleagues quantify the contribution of alignment uncertainty to genome-wide evolutionary analyses and report that we sweep this uncertainty under the proverbial rug at our peril (*1*).

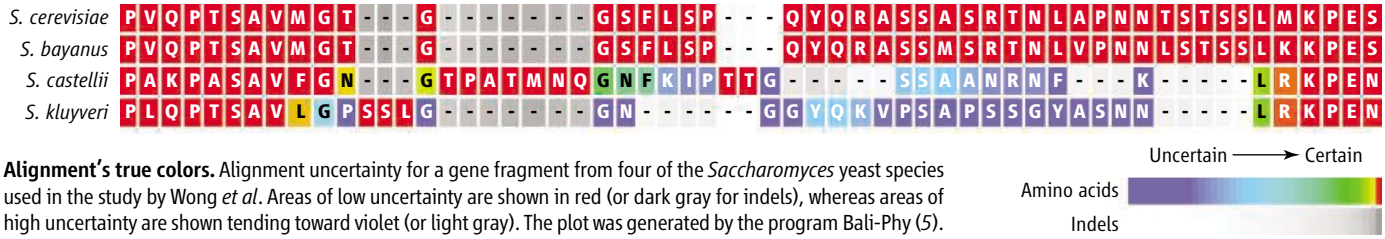
Using yeast data, Wong *et al*. collected 1502 different genes across seven genomes and aligned each of them using seven popular programs. The term "popular" is not used lightly here; these programs have been employed, judging by citation counts, in at least 25,000 analyses. To assess whether the choice of alignment method affects evolutionary analyses, the authors generated gene phylogenies and predicted the amino acid acid changes driven by selection for every possible gene by alignment combination. They report that a staggering 46.2% of the genes examined exhibit variation in the phylogeny produced dependent on the choice of alignment method, whereas the prediction of the amino acid changes driven by selection was likewise method dependent for another 28.4% of the genes.

One potential, and perhaps trivial, explanation is that certain alignment methods are particularly error-prone, thus inflating their impact. However, examination of the inferred phylogenetic trees and amino acid changes driven by selection revealed that all alignment methods contributed substantially to the sensitivity of evolutionary analyses to the choice of method. A case in point is the gene YPL077C, whose seven alignments produced six different phylogenies. Furthermore, a Bayesian measurement of alignment variability (see the figure) (*5*) was significantly correlated with the variability in phylogenetic inference. Consequently, these results argue that the observed uncertainty in inference is likely explained by the fact that some genes were much more difficult to align than others and thus challenging to all alignment methods.

Should we all revisit our evolutionary studies because we haven't properly accounted for uncertainty in alignment? Some of the disagreements observed across the molecular evolution and comparative genomics literature may be the result of alignment differences, but there is good news too. To begin with, several popular markers for evolutionary analyses became popular in the first place because they are easy to align. These genes are unlikely to exhibit variation in alignment and hence unlikely to be affected by the results of Wong *et al*., although this is not always so (*4*). Furthermore, the authors show that when the seven alignment treatments per gene result in two or more phylogenetic trees, the resulting trees rarely receive high "bootstrap" values (*1*), a popular index that uses resampling with replacement to measure robustness in inference. In other words, high bootstrap values may serve as a proxy to weed out artifactual groupings stemming from alignment uncertainty, although bootstrap values do not always equate with phylogenetic accuracy (*6*).

But what about all the other genes that are harder to align? One popular approach has been to exclude areas of uncertain alignment, and programs exist that do just that (*7*). Whether the application of such "filters" reduces the alignment-generated incongruence is currently unknown, although exclusion of all sites containing indels in the 1502 gene set does not appear to alleviate uncertainty (*1*).

In any case, filtering is unsuitable for studies where information from every site is potentially informative, or for studies of selection where fast-evolving sites may be precisely those that are the most difficult to align. To tackle analyses of such data sets, several novel statistical methods that simultaneously estimate alignment and evolutionary parameters of interest such as phylogeny have shown exceptional promise (*5*, *8*, *9*). These methods allow us to replace single best alignments by alignment distributions representing our cer-



Alignment's true colors. Alignment uncertainty for a gene fragment from four of the *Saccharomyces* yeast species used in the study by Wong *et al*. Areas of low uncertainty are shown in red (or dark gray for indels), whereas areas of high uncertainty are shown tending toward violet (or light gray). The plot was generated by the program Bali-Phy (*5*).

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tainty, or otherwise, about them. But there's a catch: The computational demands of these programs are prohibitive.

As in any scientific field, molecular evolution has a long tradition of dramatic transformation. The development of a powerful computational and statistical arsenal to account for the uncertainty stemming from sequence alignments is heralding the first paradigm shift in the era of genome-scale analysis.

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SYSTEMS BIOLOGY

Enlightening Rhythms

Ovidiu Lipan

How yeast systematically respond to environmental change emerges from blending engineering, mathematical, and experimental analyses.

We live in a sea of vibrations, detecting them through our senses and forming impressions of our surroundings by decoding information encrypted in these fluctuations. Such periodic phenomena range from circadian oscillations in living cells (*1*) to acoustic oscillations in the primordial universe (*2*). Passively observing periodic phenomena is scientifically rewarding, but actively using periodic stimuli to observe the hidden wonders of nature is even more so. On page 482 of this issue, Mettetal *et al.* (*3*) report using oscillatory stimuli to decipher how an organism—the yeast *Saccharomyces cerevisiae*—responds to environmental changes. By constructing a predictive mathematical model for specific signaling pathways (*4*), they show that oscillatory stimuli can be used to study how networks of proteins and genes are engaged by a living system to control physiological behavior.

Many scientific studies hinged on creating oscillations to study natural systems. The idea of electromagnetic waves was implicit in James Maxwell's theory, but it was Heinrich Hertz's electric oscillators that created and measured their properties, thus confirming light waves as electromagnetic radiation, the most striking victory of 19th-century experimental physics (*5*).

Although the use of oscillatory stimuli to study how networks of proteins and genes regulate gene expression is theoretically valuable (*6*), implementation of this procedure is not obvious because the possibilities for constructing genetic oscillators are limited, at present. It takes ingenuity to find a molecular pathway that responds to an oscillatory signal, much less an experimental procedure to create these oscillations. Furthermore, these oscillations must produce detectable responses. Mettetal *et al.* fulfill these constraints by studying a signaling pathway in yeast that responds to changes in environmental osmolarity. Glycerol is the main yeast osmolyte and its concentration is controlled in part by the high-osmolarity glycerol (HOG) signaling pathway that involves the enzyme Hog1. By adjusting the export rate of glycerol through the cell membrane, yeast maintain osmotic balance.

Mettetal *et al.* studied three negative-feedback loops of the HOG pathway. One loop controls glycerol concentration through the membrane protein Fps1, and depends on the amount of active Hog1 in the nucleus. A second loop also involves Fps1, but is controlled by osmotic pressure across the cell's membrane and the concentration of intracellular glycerol. A third loop is Hog1 dependent and acts on glycerol concentration by increasing the expression of genes encoding the glycerol-producing proteins Gpd1 and Gpp2.

Which of the three negative-feedback loops dominate the dynamics of this osmo-adaptation system? Can system identification methods, such as those used by robotics engineers, describe the signaling dynamics of the dominant negative-feedback loops? To apply systems engineering methods, an input signal must be created and an output response signal must be recorded. Mettetal *et al.* varied the concentration of sodium chloride in the cell media, thus exposing cells to square-wave pulses (alternating between two values for an equal amount of time) of osmotic pressure. The output response recorded was the ratio between nuclear-localized, active Hog1 and Hog1 within the entire cell.

For designing complex systems, a success is claimed if the output response of a system to an external input signal can be mathematically predicted. Viewed only in terms of its input and output characteristics, the osmo-adaptation pathway loses its inner biological structure and becomes what is referred to as a "black box." The authors developed a black-box mathematical model for the osmo-adaptation pathway. They estimated parameters of the model from measurements using square-wave pulses of variable frequencies, then validated the predictive power of the model using a step input—one that switches on at a definite time and remains on indefinitely—of sodium chloride. Because gene regulatory networks contain many unknown molecular components, a black-box mathematical model is the best achievable solution in various situations.

Variable frequencies. Oscillating signals may unlock the complex organization of organisms.

The ultimate goal, however, is a mathematical model for a white box, in which all the molecular components and their interactions are known. The road toward this goal is paved with intermediate gray-box models containing some biological inner structures. Toward this end, Mettetal *et al.* transform the black-box mathematical model into a gray one that successfully incorporates the first two of the three osmo-adaptation feedback loops described. In doing so, they discovered that the dynamics of the osmo-adaptation response are dominated by the fast-acting Hog1-dependent negative feedback loop that does not require a change in gene expression.

The hope is to include other molecular components and feedback loops into a

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more detailed mathematical model. This will require new techniques to generate molecular input signals—perhaps based on photons rather than chemicals—for tuning gene expression and protein degradation (*7*, *8*). The study by Mettetal *et al*. is part of a large effort to blend the biological and mathematical structure of living systems and understand living systems not as collections of machine parts, but as stable, complex dynamic organizations (*9*). Hopefully, 21st-century systems biology will claim victories as striking as those of Maxwell and Hertz.

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GEOCHEMISTRY

The Rise and Fall of a Great Idea

Heterogeneities in Earth's mantle create ambiguity about the origin of hot-spot lavas.

Anders Meibom

On page 453 of this issue, Luguet *et al.* address a key question in geology (*1*): Can we determine the provenance of hot-spot lavas by geochemical means? The authors show that the chemistry of Earth's mantle is too heterogeneous to allow the detection of chemical or isotopic signatures of the "mantle plumes" widely held to cause hot-spot volcanism (see the figure).

For decades, mantle geochemists have tried to find a clear isotopic or chemical signature of Earth's outer core in oceanic basalts, which are produced along mid-ocean ridges or at isolated, intraplate islands such as the Hawaiian chain. The latter are often assumed to be associated with deep-rooted upwellings called mantle plumes. Detection of a geochemical signature unambiguously linked with the outer core in such an intraplate basalt would make a very strong case for mantle plumes that originate at the core-mantle boundary (~2900 km below the surface). This would, in turn, have important implications for our understanding of large-scale mantle convection, the long-term stability of different mantle regions, and other fundamental aspects of Earth's interior.

The platinum-osmium (Pt-Os) and rhenium-osmium (Re-Os) isotopic systems have played a dominant role in these studies. ^{190}Pt is a rare platinum isotope that decays to ^{186}Os with a very long half-life of ~450 billion years. ^{187}Re is the most abundant rhenium isotope and decays to ^{187}Os with a half-life of ~42 billion years. Over time, a system with fractionated (that is, changed) Pt/Os and Re/Os elemental ratios will develop ^{186}Os/^{188}Os and ^{187}Os/^{188}Os ratios that are different from those in a system in which these elements were not fractionated. (The stable isotope ^{188}Os is used for normalization.)

Earth's mantle was strongly depleted in osmium, platinum, and rhenium during core formation, because these elements tend to move into metallic phases. If the osmium concentration is much higher in the liquid outer core than in the surrounding mantle, mixing a little bit of outer-core material back into the mantle at the core-mantle boundary will change the local osmium isotopic composition to resemble that of the outer core. And if the osmium isotopic composition of the outer core is very different from that of the upper mantle, it might be detected in lavas brought to Earth's surface.

This is a great idea. Excitement therefore followed the discovery of enhanced ^{186}Os/^{188}Os and ^{187}Os/^{188}Os ratios in Hawaiian basalts; a case was made for an outer-core origin of this isotopic signature (*2*). The logic was that the measured osmium isotopic ratios, particularly ^{186}Os/^{188}Os, would not normally exist in the mantle, but that inner-core solidification could produce the required fractionation of osmium, platinum, and rhenium in the remaining outer core. Finally, geologists had what looked like proof of a deep origin of a proposed mantle plume.

But as the assumptions behind the model were examined, problems appeared. First, modeling of osmium, platinum, and rhenium fractionation between the solidifying inner core and the molten outer core is largely unconstrained. We do not know with certainty either the light-element composition of the outer core or the crystal structure of the solid inner core. We know even less about the fractionation behavior of these elements between the inner and outer core.

Mantle complexities. Thermally driven upwellings in the mantle—so-called mantle plumes—are often envisioned to originate at the core-mantle boundary, from which they rise to create the hot-spot volcanism seen, for example, in Hawaii. Unambiguous geochemical signatures of the outer core in such hot-spot basalts would prove the existence of deep-rooted mantle plumes, with important implications for large-scale mantle dynamics. But the detection of geochemical signatures uniquely tied to the outer core is severely complicated by a very high degree of upper-mantle heterogeneity, as shown by Luguet *et al*.

Second, when the fractionation of osmium, platinum, and rhenium between the inner and outer core was tuned in the model to fit the data from the Hawaiian basalts, the extremely long half-life of ^{190}Pt required the inner core to have started to crystallize early in Earth's history. This conclusion is in direct conflict with geophysical studies of the evolution of the inner/outer core system (*3*).

Third, an osmium isotopic signature from the outer core should be accompanied by a distinct signature in the isotopic composition of tungsten. This signature was not found (*4*).

Finally, osmium isotopic analyses of other mantle-derived materials showed that the upper mantle is very heterogeneous and that the Os isotopic "anomalies" detected in the Hawaiian basalts were probably not that anomalous (*5*). For example, certain mantle sulfides could have the appropriate Pt/Os and

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Re/Os fractionations to develop the observed ^{186}Os and ^{187}Os enrichments (*5*, *6*), although data supporting such a model were sparse.

Luguet *et al.* now provide the chemical and isotopic data to support this model. Their results radically change the basis on which osmium isotopic compositions from mantle-derived materials are evaluated. There is no longer a need to invoke an outer-core input to explain the osmium isotopic compositions of mantle-derived materials. And there is no geochemical smoking gun for a core-mantle boundary origin of the Hawaiian intraplate volcanism. Instead, there is evidence for a very high degree of geochemical heterogeneity in the upper mantle. This is not only true for the osmium isotopic systems; it seems to be generally true and has important consequences for explaining the origin of isotopic "anomalies" in mantle-derived materials.

Geochemical heterogeneity is introduced into the mantle, for example, by subduction of sediments, oceanic crust, and lithosphere, and by melt extraction. Other processes can also contribute to the creation of a range of geochemical components in the upper mantle. All these processes redistribute (fractionate) major and trace elements among different minerals, fluids, and melts, which in turn allows different components to evolve along divergent isotopic trajectories.

The concept of isotopic "anomalies" in oceanic basalts thus has to be applied with extreme care. Indeed, with an upper mantle as heterogeneous as the data by Luguet *et al.* suggest, it is difficult to imagine that isotopic signatures in oceanic basalts can be uniquely tied to the outer core. The debate about the existence and possible origins of deep-rooted mantle plumes will most likely have to be settled with geophysical methods.

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MATERIALS SCIENCE

Structural Nanocomposites

Reinforcement of small structures and critical volumes with nanomaterials may enable near-term applications that can drive longer-term research.

Yuris Dzenis

Materials scientists predict that composites made with nanoscale reinforcing materials such as nanotubes, platelets, and nanofibers will have exceptional mechanical properties. However, the results obtained so far are disappointing, particularly when compared to advanced composites reinforced with high-performance continuous fibers (*1*–*4*). The reasons include inadequate dispersion and alignment of the nanoreinforcement, low nanoreinforcement volume fraction, and poor bonding and load transfer at interfaces. Intensive work is under way, but the prospect of bulk structural supernanocomposites appears more remote now than it did just a few years ago. However, recent work shows that some applications in reinforcement of small structures may have a near-term payoff that can foster longer-term work on nanocomposites.

Most of the work on structural nanocomposites has relied on ultrastrong nanoreinforcement such as single-walled carbon nanotubes (SWCNTs) (*1*–*3*). However, the high SWCNT strength has not yet translated into bulk strength, and it is not even clear whether such translation is possible: Any attempt to create strong interfacial bonds will introduce defects into the SWCNTs that reduce their intrinsic strength. Still, multifunctional applications not relying solely on the mechanical superproperties will benefit (*4*, *5*). Tailorability and controlled anisotropy are other useful special features of nanocomposites. Multiscale modeling (*6*) will help us achieve the desired balance between various functions.

One frequently overlooked characteristic of nanoreinforcement is its small size. Various miniature and confined structures can benefit from the improved performance and tailorability of nanocomposites, including ultrathin coatings, membranes, films, and fibers; dental prostheses; structural elements in micromachines and micro- and nanoelectromechanical systems (MEMS/NEMS); thin walls in foams and aerogels; and connections in microcircuits. With the notable exception of nanoreinforced fibers (*1*, *2*), work on the use of nanoreinforcement in microstructures has been slow, but progress is expected to accelerate with the development of more robust nanomanufacturing processes.

Another promising area of research involves solving structural problems that occur in small critical volumes, especially weak spots requiring nanoreinforcement and regions with high localized stress concentrations. Various microdefects and weak inclusions or inhomogeneities represent the former type, whereas sharp structural corners and crack tips are examples of the latter. Cases where both conditions occur simultaneously are the best candidates.

The use of nanocomposites in microscopic structures or critical volumes requires careful multiscale structural design as well as development of techniques to incorporate the nanocomposite in the desired microcomponents. Although the challenges may be great, the resulting applications can be achieved

A pathway to supernanocomposites? (**Left**) Advanced laminated composite with nanofiber-reinforced interfacial layer. (**Right**) In situ observation of interlaminar toughening nanomechanisms including Velcro-like crack bridging by nanofibers.

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with considerably lower cost relative to the bulk applications, while providing substantial improvements in the overall structural performance by applying the nanoreinforcement where it is most needed and/or where there are no alternatives.

On the basis of these principles, my colleagues and I created an advanced laminated composite with nanoreinforced interfaces (*7*). Delamination is a severe and persistent problem in laminated composites made of anisotropic fiber-reinforced plies (*8*). High interlaminar peel and shear stresses near edges initiate delamination cracks that propagate along the nonreinforced interlaminar planes with little resistance. Delamination substantially reduces the load-carrying capacity and durability of advanced composites and has led to disastrous structural failures. Since the discovery and explanation of the mechanisms of delamination in advanced composites in the early 1970s, researchers have tried to improve delamination resistance. Most designs, however, resulted in cost and weight penalties.

Nanofibers or nanotubes can be used to reinforce interfaces in advanced laminated composites (*7*) (see the figure). Entangled nanofibers improve interlaminar fracture resistance much like the hooks and loops in Velcro. Experiments with advanced aerospace-grade carbon-epoxy composites showed that a minute quantity (less than 1% by weight) of polymer nanofibers improved the static and fatigue peel and shear interlaminar fracture toughness. We observed that crack deflection, nanofiber pull-out, plastic deformation, and crack bridging all played a part. Moreover, recent computer simulations also confirmed reduction of the edge stresses in the laminates with the nanoreinforced interfaces (*9*). These improvements are achieved without any measurable increase of weight or decrease of other composite properties. As delamination is known to have a detrimental effect on the overall composite performance (*8*), the observed improvements can be expected to lead to increases in composite strength, durability, and impact resistance.

In this and similar (*10*) hybrid nano-micro composite designs, the small-scale reinforcement strengthens the ultrathin matrix-rich layers. These microvolumes are critical for two reasons: They are weak (nonreinforced) and they experience high stress concentrations. The designed three-dimensional nanoreinforcement, with the combination of interlocked in-plane and out-of-plane nanofibers, successfully resolves both of these issues. The design may enable low manufacturing costs, as the nanofibers are used in ultrasmall quantities and their introduction into composites can be integrated with existing composite manufacturing technologies.

Other designs along these lines are possible. For example, fiber-matrix interfaces engineered with bonded nanoparticles show enhanced energy dissipation via a variety of mechanisms. Such interfaces modified by grown carbon nanotubes have exhibited increased interfacial shear strength (*1*). Nanoreinforcement of adhesive layers, contacts in sintered particulates, or grain boundaries in polycrystalline ceramics and metals can also be pursued. In general, any interface, inclusion, inhomogeneity, or interstitial volume in heterogeneous materials represents a promising nanocomposite application. This should lead the use of nanomaterials as nanoreinforcement in the near- and medium-term time frames, while providing impetus for the long-term development of bulk structural supernanocomposites.

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MATERIALS SCIENCE

Adaptive Composites

Richard Vaia and Jeffery Baur

Materials are under development that can respond dynamically to changes in their environment.

Imagine a search-and-rescue robot that can change shape to squeeze through crevices with the suppleness of an octopus, or an aircraft skin with a circulatory system that enables temperature regulation, cooling, and self-healing similar to an animal. Such concepts are driving the development of adaptive composites that mimic biological responsive functionality while operating in extreme environments.

Traditionally, the high-performance, load-bearing substructures of aircraft, satellites and robots are designed for structural efficiency. Thus, they are rigid and passive; active functions such as sensing, energy harvesting, and propulsion are added by attaching components to the structure. This compartmentalization of functions into attached subsystems streamlines manufacturing and maintenance and facilitates upgrades (*1*). Advanced passive material technologies, such as continuous-fiber organic-matrix composites, have revolutionized applications from sporting equipment and prosthetics to satellites and aircrafts.

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However, this approach is in stark contrast to natural organisms, in which flexible, jointed frameworks and complex materials impart active functionality at multiple length scales within the materials (see the figure). The realization of analogous synthetic structures depends on the combination of new materials that deliver active properties and autonomic response, as well as new computational tools that enable design, analysis, and optimization of the collective and hierarchical dynamic character.

The transformation of a rigid substructure to a dynamic, articulated structure is particularly interesting for the aerospace industry. Large-scale actuated bending, extending, and folding structures would enable the deployment of large-scale antennae in space and the development of morphing wings on unmanned aerial vehicles. Other applications for new adaptive materials include energy-efficient locomotion and concealment.

Materials with reversible property changes—such as piezoelectric ceramics—have been studied for at least 100 years (*2*), but these materials have been monolithic. In contrast, new multicomponent, hierarchical material systems are inspired by biology. For example, a cell's ability to change shape and recover

from large deformations arises in part from the arrangement of actin filaments in the cellular cytoplasm (*3*). Similar highly deformable networks can be created from cellular materials, bistable composite laminates, and bimorph strips. Alternatively, the elastic buckling of carbon nanotube mats (*4*) and arrays (*5*) may be used to store and recover substantial amounts of strain energy.

Combining these concepts with materials that exhibit a reversible stiffness enables trapping and subsequent release of the mechanical deformation. For example, the stiffness of shape-memory polymers can be reversibly changed between a thermoplastic glass and an elastomer when triggered (by temperature or other means) and will "remember" their original shape as they are softened. Studies on the International Space Station recently showed that hinges made from an elastic memory composite (consisting of predeformed carbon fibers in a shape-memory polymer matrix) are a viable replacement for current complex mechanical hinges used for unfurling structures such as solar arrays (*6*).

Reversibility needs to be triggered easily and controllably. The trigger for mechanical property changes is usually temperature, which can limit the speed of the transition and complicates control systems. Recent demonstrations of other triggering stimuli have broadened the suite of possible control concepts.

For example, Baughman and co-workers used a coating of catalytic nanoparticles on a shape-memory alloy wire to convert enough chemical energy to thermal energy to trigger a shape recovery of the wire (*7*). Advances in understanding natural systems are also highlighting chemical triggers. For example, addition of acetylcholine and calcium ionophores shifts the iridescence of the mantle iridophores of the cephalopod *Lolliguncula brevis* from red to blue, providing dynamic coloration. Recombinant derivatives of comparable proteins have been self-assembled in vitro to form fibers and diffraction gratings with dynamic coloration (*8*).

Radiation can also be used as a trigger for adaptive response. Recent advances in optically triggered, reversible colloid surface chemistry (*9*) may lead to rheological fluids that do not require a bias to maintain an ordered electrical or magnetic state. Photoisomerization on the molecular scale can alter liquid-crystal phase stability or control domain orientation, resulting in substantial changes in mechanical and optical characteristics (*10*). Koerner and co-workers used carbon nanotubes dispersed in shape-memory polymers to trigger shape recovery both electrically and optically (*11*). Finally, Buckley and co-workers have presented a scheme for shape-changing medical devices activated by radio-frequency radiation (*12*).

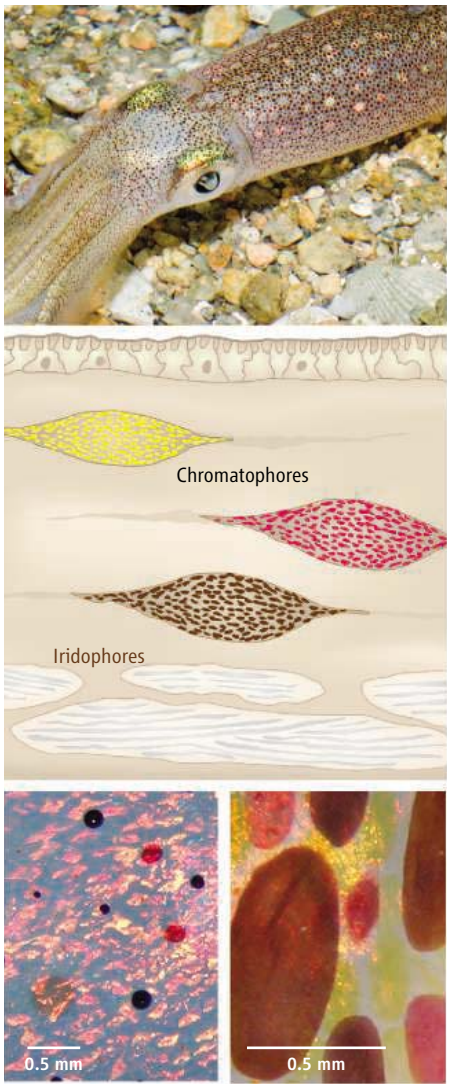
Materials for adaptive composites need not be restricted to solid constituents, but can incorporate fluid networks. For example, Sottos and co-workers have developed a self-healing system based on a three-dimensional microvascular network embedded in the substrate (*13*). The network autonomously delivers a healing agent to repair cracks in a damaged polymeric surface sheet.

Natural systems also provide inspiration for design and pumping concepts for circulation. For example, the heart of the zebra fish efficiently pumps fluids along a longitudinally graded channel via resonate coupling of an excitation. Also, the xylem and phloem vessels of vascular plants exemplify the benefits of axially graded channel walls.

By including fluids and associated mass transport within a composite, many active functions—such as thermal management, variable modulus, and dynamic optical transmission—can be envisioned. However, the use of fluids also poses substantial challenges, because the resulting materials are more complex and less durable. For example, pores and voids are known to drastically reduce strength in engineered materials. However, recent reports indicate that the strength and toughness of composites is less impacted by embedded channels than by voids that form during processing (*14*).

Even with this ever-expanding array of material concepts, adaptive composites will fall short of their perceived potential without the development of verified, validated, and streamlined computational design tools that capture the properties of the many possible configurations or states. Further complexity arises in considering control concepts for these multiple active materials.

Alternative concepts such as emergent, morphogenic, or evolutionary design may be best adapted to deal with this complexity. For example, Stoy and Nagpal have provided elegant computational examples of how a set of local control rules can be used to construct mobile robots or self-repairing structures from discrete reconfigurable pieces (*15*). The challenge is how to harness these concepts with the process and fabrication tools of materials science and nanotechnology.



Inspired by biology. The communication and camouflage of squids (*Loligo pealeii*, **top**) arises from a precise arrangement of organelles in an elastomeric skin (**middle**). Chromatophores modulate adsorption by laterally swelling (**bottom, left to right**), while iridophores modulate reflections (iridescence) through swelling an effective Bragg grading. Scientists are now attempting to realize composite materials that reproduce the performance of such biological systems. [Adapted from (*16*)]

PHOTO CREDITS: (TOP) ROGER HANLON/MARINE BIOLOGY LABORATORY, WOODS HOLE, MA; (BOTTOM PAIR) LYDIA MATHGER/MARINE BIOLOGY LABORATORY, WOODS HOLE, MA

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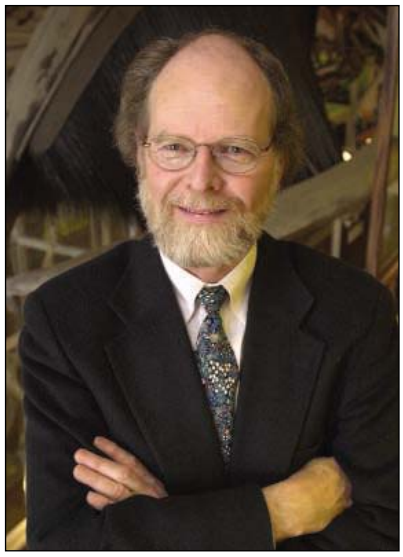
ASSOCIATION AFFAIRS

McCarthy: Share the Excitement of Discovery with the Public

The world's oceans are restless, wide-ranging, and unconcerned with borders—and they may have met their match in James McCarthy. Early in his career, he was drawn to oceanography as a chance to "work across boundaries," delving into biology, chemistry, and geology in waters around the globe. As he assumes the AAAS presidency in February, he sees the future of science similarly driven by interdisciplinary research, outreach to scientists in developing nations, and the intersection of science and policy to address international issues.



James McCarthy

Global climate change is one such issue that has occupied McCarthy for decades, starting with his own research interests in marine plankton and biogeochemical cycles, and extending to his leadership in national and international groups such as the International Geosphere-Biosphere Program and the Intergovernmental Panel on Climate Change (IPCC), and as the Alexander Agassiz Professor of Biological Oceanography at Harvard University.

"I've spent much of my time for the last 25 years working to bring groups of scientists together who had historically worked alone in their own disciplinary communities, to work across boundaries to generally explore common territory and look for exciting new directions in science," he said in an interview.

McCarthy said his work on climate change has drawn him inevitably across the research border toward science policy and science education, where he sees many opportunities to strengthen the ties between science and society. In particular, he says, scientists need to be better at communicating the exciting nature of their profession to young people.

"It's very interesting talking to high school and college students about the problems that we face today with respect to climate change, the realization that everything we know that makes this problem urgent has been discovered in their lifetime," he said. Unfortunately, he added, many young people see science as a static set of textbook facts rather than a dynamic process.

"We often underestimate the 'wow!' factor, the realization that those of us who have decided to spend our careers in science are every day finding something exciting," he noted, joking that "it's certainly very different from the way most of my colleagues would describe their careers in business or law or in medicine."

McCarthy thinks that working with science museums, giving public lectures, and contributing science coverage in the media are all ways that researchers can increase the public's appreciation of science. But he acknowledged that the press and scientists "come from different cultures" and are not always natural allies.

"I like to think that when I talk to a person from the press, it's not a source and a reporter interacting, it's two of us together on an educational mission," he explained. "And that's tough to sell, because some people in the press say no, science is just another interest group and you're trying advance your hobby horse."

He is adamant about the fact that science is not "just another special interest group," a characterization he's also encountered when testifying before the U.S. Congress. Too often, McCarthy said, politicians dismiss a scientist's testimony as "just your idea," and miss the fact that "science is based on evidence. They don't appreciate that science is not simply a collection of ideas, and that scientists only maintain their scientific excellence by constantly questioning, constantly being skeptical, and always being open to new evidence and new interpretations of evidence."

"One of the realizations of this [U.S. presidential] election year is that we really must restore the scientific integrity of our federal government," McCarthy said. He suggested that the scientific community has been "distressed" in recent years to see federal reports in which "the best representations of science performed by experts widely revered in their field…have been edited, and clearly by people who did not know or understand the science, but who didn't like the message."

McCarthy is heartened by the fact that many of the U.S. presidential candidates from both major parties have accepted the research consensus on global climate change and have included climate policy proposals in their campaign platforms. "But the formulation of the policy needs more information than just, 'we have a problem.' And here the scientific and engineering communities have a very important role to play," he said.

In December, the U.S. Congress voted on an omnibus appropriations bill that would fund federal research and development at levels far below what was expected for fiscal year 2008. Researchers should argue strongly for the larger economic benefits of R&D, McCarthy suggested. While he doesn't "have any illusions that the new president will magically be able to dig us out of the hole we're in right now," he urged that "the science community must be ready to help a new Administration in any way we can."

AAAS "is very keen" to build on the theme of this year's Annual Meeting, "Science and Technology from a Global Perspective," and find more ways to support the travel and professional expenses of researchers from developing nations, McCarthy said. His own work with the IPCC convinced him that the organization's reports "could not have had the success that they did without the participation of developing nations."

McCarthy will succeed the current president, Nobel laureate David Baltimore of the California Institute of Technology, at the close of the 2008 Annual Meeting on 18 February. Baltimore will become chair of the AAAS board as John Holdren, director of the Woods Hole Research Center and Teresa and John Heinz Professor of Environmental Policy at Harvard University, steps down. Peter C. Agre has been elected to succeed McCarthy as president-elect. Agre, a 2003 Nobel laureate, is the director of the Malaria Research Institute in the Johns Hopkins University Bloomberg School of Public Health.

—Becky Ham

SCIENCE POLICY

Project Tracks S&T in '08 Presidential Campaign

As the U.S. presidential primary campaigning builds to high intensity across the country this winter, AAAS has launched a new Web site devoted to science and technology issues in the 2008 election.

Science and Technology in the 2008 Presidential Election, at http://election2008.aaas.org, highlights five S&T issues to watch in the election year: competitiveness and innovation; education and the workforce; health care; energy and the environment; and homeland security.

The site also features the candidates' positions on the major S&T issues, including relevant news stories and published commentaries; survey information; white papers and other reports from policy organizations; and election calendars.

Although some candidate Web sites feature extensive S&T platforms, these detailed plans have yet to become a key feature in any campaign. During the primary campaign, "the treatment of science-related issues has ranged from superficial to nonexistent," AAAS CEO Alan I. Leshner wrote in a 4 September 2007 op-ed in the *Des Moines Register*.

With a grant from the Richard Lounsbery Foundation, AAAS's Center for Science, Technology, and Congress developed the new site as a resource for voters to explore the candidates' S&T positions, and to provide the research community with a vehicle for informing the candidates on emerging issues. CSTC and its partner in the site, the Association of American Universities (AAU), plan to contact the various presidential campaigns to encourage them to suggest relevant content for the site.

"As science and technology issues become a part of the political debate in 2008, it is important that voters have access to as much information as possible about the candidates and their views," said CSTC Director Joanne Carney. "We hope the project will provide this information, give the candidates access to voters who care about these issues, and engender a much-needed dialogue about science, technology, policy, and politics."

The project is the result of an informal working group composed of representatives from the AAU, Woodrow Wilson International Center for Scholars, Center for the Study of the Presidency (CSP), National Academies, and other organizations. Meeting last year, the group urged the scientific community to get more involved in political dialogues and encourage the candidates to discuss S&T during their campaigns.

"In previous elections, science issues have been reduced to one or two hot-button items, with no real discussion of how candidates would utilize science in their administration," said AAU President Robert M. Berdahl. "But the 21st century will witness a worldwide competition for scientific and technological mastery, and it is our hope that the site will help voters determine how candidates would meet this challenge."

Carney said the new site was also motivated in part by a study released jointly by CSP and AAAS, prepared as a report to the U.S. president-elect in the fall of 2000. The report, *Advancing Innovation: Improving the S&T Advisory Structure and Policy Process*, included discussions from a conference by AAAS and CSP on science policy, presidential leadership, the evolution of the White House Office of Science and Technology Policy, and the importance of congressional support for basic science research. The report eventually became part of a six-volume CSP series delivered to the president-elect that highlighted pressing issues for the coming executive term.

A special News Focus section in the 4 January issue of *Science* profiled the leading Republican and Democratic presidential candidates and their stances on science issues such as global climate change, stem cell research, and innovation.

—*Benjamin Somers and Becky Ham*

ANNUAL MEETING

Scientists Convene in Boston to Build World Partnerships

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world."
—Louis Pasteur

Researchers, journalists, and the public can explore the world of science and its influence on the world through interdisciplinary studies and emerging policy issues presented at the 175th AAAS Annual Meeting in Boston next month, "Science and Technology from a Global Perspective."

This year's program includes more than 150 symposia and special lectures on topics ranging from climate change, infectious disease, technology in developing nations, and emerging international collaborations among researchers. Parents, teachers, health educators, and the public are invited 17 February to a special Town Hall on childhood nutrition and obesity trends around the world.

In his invitation to the meeting, AAAS President David Baltimore said the conference will highlight the power of science, technology, and education "to assist less developed segments of world society while also improving cooperation among developed countries and spurring knowledge-driven transformation across scientific disciplines."

The AAAS Annual Meeting Blog will provide extensive coverage from Boston, featuring reports and podcasts from the staff of ***Science*** and ***ScienceNOW***, AAAS's award-winning Science Update radio program, and AAAS's writers, along with links to U.S. and international news coverage of the meeting. For registration and other information about this year's meeting, see www.aaas.org/meetings.

SCIENCE AND TECHNOLOGY FROM A GLOBAL PERSPECTIVE

AAAS

Call for Nomination of 2008 AAAS Fellows

AAAS Fellows who are current members of the association are invited to nominate members for election as Fellows. A Fellow is defined as a member "whose efforts on behalf of the advancement of science or its applications are scientifically or socially distinguished." A nomination must be sponsored by three AAAS Fellows, two of whom must have no affiliation with the nominee's institution.

Nominations undergo review by the steering groups of the association's sections (the chair, chair-elect, retiring chair, secretary, and four members-at-large of each section). Each Steering Group reviews only those nominations designated for its section. Names of Fellow nominees who are approved by the steering groups are presented to the AAAS Council for election.

Nominations with complete documentation must be received by 9 May 2008. Nominations received after that date will be held for the following year. The nomination form and a list of current AAAS Fellows can be found at www.aaas.org/aboutaaas/fellows. To request a hard copy of the nomination form, please contact the AAAS Executive Office, 1200 New York Avenue NW, Washington, DC 20005, USA, at 202-326-6635, or at btucker@aaas.org.

PRESIDENTIAL ADDRESS

Science and Technology for Sustainable Well-Being

John P. Holdren

The American Association for the Advancement of Science (AAAS) is not about the advancement of science just for science's sake. Rather, as indicated by the Association's motto, "Advancing Science, Serving Society," it is about advancing science in the context of a desire to improve the human condition. This mission necessarily entails attention to the social as well as natural sciences; attention to the embodiment of science in technology through engineering; and attention to the processes by which understandings from the natural sciences, the social sciences, and engineering influence—or fail to influence—public policy. All of these long-standing preoccupations of the AAAS are integral to the theme of the 2007 Annual Meeting and of this essay, "Science and Technology for Sustainable Well-Being."

I begin my exploration of that theme with some premises and definitions relating to well-being and sustainability, before turning to a taxonomy of shortfalls in sustainable well-being and a rough quantification of those that are reflected in morbidity and mortality. I then address the status of five specific challenges in which science and technology (S&T) have particularly important roles to play: meeting the basic needs of the poor; managing the competition for the land, water, and terrestrial biota of the planet; maintaining the integrity of the oceans; mastering the energy-economy-environment dilemma; and moving toward a nuclear weapon–free world. I close with some thoughts on what more is needed in order to improve the pace of progress, including what the AAAS is doing and can do and what individual scientists and engineers can do.

Well-Being and Sustainability

Human well-being rests on a foundation of three pillars, the preservation and enhancement of all three of which constitute the core responsibilities of society:

•*Economic conditions and processes*, such as production, employment, income, wealth, markets, trade, and the technologies that facilitate all of these;

•*Sociopolitical conditions and processes*, such as national and personal security, liberty, justice, the rule of law, education, health care, the pursuit of science and the arts, and other aspects of civil society and culture; and

•*Environmental conditions and processes*, including our planet's air, water, soils, mineral resources, biota, and climate, and all of the natural and anthropogenic processes that affect them.

Arguments about which of the three pillars is "most important" are pointless, in part because each of the three is indispensable: Just as a three-legged stool falls down if any leg fails, so is human well-being dependent on the integrity of all three pillars.

The futility of attempts to strengthen any one of the pillars in ways that dangerously weaken one or both of the others is underlined by their interdependence. The economic system cannot function without inputs from the environmental system, nor can it function without elements of societal stability and order provided by the sociopolitical system. And societal stability itself cannot be maintained in the face of environmental disaster, as the effect of Hurricane Katrina on New Orleans demonstrated is true even in the most economically prosperous and technologically capable country in the world.

This understanding about the elements of well-being leads, when combined with the proposition that improvements in well-being are most meaningful if they can be sustained, to a set of definitions that embody the essence of the sustainable-well-being challenge (*1*):

•*Development* means improving the human condition in all of its aspects, not only economic but also sociopolitical and environmental;

•*Sustainable development* means doing so by means and to end points that are consistent with maintaining the improved conditions indefinitely; and

•*Sustainable well-being*, in my lexicon, entails pursuing sustainable development to achieve well-being where it is now most conspicuously absent, as well as converting to a sustainable basis the maintenance and expansion of well-being where it already exists but is being provided by unsustainable means.

Shortfalls

Persistent shortfalls in the pursuit of sustainable well-being are evident across a range of dimensions of the human condition, including (*2*):

•*Poverty*, afflicting not only the 2.5 billion people in the poorest countries who live on less than the equivalent of $2 per day, but also hundreds of millions in addition who have much more but still cannot afford many of the ingredients of a decent existence in the more prosperous settings in which they live;

•*Preventable disease*, which keeps infant and child mortality high and life expectancy low, especially in Africa but among the very poor everywhere;

•*Impoverishment of the environment*, meaning progressive erosion of the environmental underpinnings of well-being in the qualities of air, water, soil, biota, and climate;

•*Pervasiveness of organized violence*, manifested in the well over 100 instances of armed conflict since World War II (nearly all of them in the South, with a total loss of life in the tens of millions), as well as in the global rise of terrorism;

•*Oppression of human rights* in other ways (for the preceding items are also forms of such oppression), denying human beings their dignity, their liberty, their personal security, and their possibilities for shaping their own destinies; and

•*Wastage of human potential*, resulting from all of the foregoing and the despair and apathy that accompany them, from shortfalls in education, and from the loss of cultural diversity.

Underlying these shortfalls is an array of driving forces and aggravating factors, among them:

•*Non-use, ineffective use, and misuse of S&T*, including misuses both intentional (as in the development and deployment of weapons of mass destruction) and inadvertent (as manifested in the side effects of broad-spectrum herbicides, pesticides, and antibiotics);

•*Maldistribution of consumption and investment*, where the maldistribution is of three kinds: between rich and poor as the beneficiaries of both consumption and investment; between military and civilian forms of consumption and investment ["too much for warfare, too little for welfare" (*3*)]; and between the two activities themselves; i.e., between too

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much consumption and too little investment;

•*Incompetence, mismanagement, and corruption*, which although sometimes attributed to developing countries particularly are in fact pervasive in industrialized and developing countries alike;

•*Continuing population growth*, which, while not the sole cause of any of the shortfalls listed, makes the remedy of all of them more difficult (*4*); and

•*Ignorance, apathy, and denial*, the first consisting of lack of exposure to information and the second and third of having the information but lacking the conviction or optimism or understanding to act on it.

The magnitudes of the contributions to premature mortality of a number of the shortfalls and their respective contributing factors are shown in Table 1, which is adapted from a remarkable compilation of the underlying causes of premature death produced by the World Health Organization (WHO) (*5*–*7*).

How Can S&T Help?

Table 1 underlines the role, in global mortality, of shortfalls in the deployment if not always the development of adequate technologies for food production, clean water and sanitation, and clean and efficient energy supply. I would characterize the roles of S&T in addressing the challenges of sustainable well-being in broader terms as follows:

•Advances in science improve our understanding of shortfalls, dangers, and possibilities and enable advances in technology.

•Advances in technology help meet basic human needs and drive economic growth through increased productivity, reduced costs, reduced resource use and environmental impact, and new or improved products and services.

•S&T together provide the basis for integrated assessment of challenges and opportunities, advice to decision-makers and the public about these, and formal and informal education toward a more S&T-literate (and therefore more informed and capable) society.

The need to do better with S&T applied to the goal of sustainable well-being is particularly compelling in relation to the five specific challenges mentioned above, and I turn to these now.

Meeting the Basic Needs of the Poor

The contemporary effort to address this most fundamental of sustainable-development needs is cataloged and chronicled in the Millennium Development Goals (MDG) project of the United Nations (UN). The MDGs, consisting of eight overarching goals and specific targets for the pace of progress to be made on them, were officially adopted in 2000. The goals, targets, and some indicators of the extent of progress on them are summarized in Table 2. The MDG picture is clearly mixed. Many regions are on track to meet many of the targets, but other regions—and above all sub-Saharan Africa—are projected to fall short on most of them. What is worse, while the MDGs appear ambitious in terms of the pace of improvement embodied in the targets, they are really very modest when viewed in terms of the immense shortfalls in well-being that would persist into 2015 and beyond even if the targets were met. Where the targets do seem likely to be met for the world as a whole, moreover, as is the case for access to safe drinking water, regional shortfalls still loom large (*8*).

The considerable progress that has been made in some important respects (such as in life expectancy, which has been improving virtually everywhere other than sub-Saharan Africa and the former Soviet Union) has been the result of a combination of economic and social factors, but improvements in technology appear to have been the most important (*9*). Among other advances, widespread gains in the productivity of agriculture, which played a crucial role in improving nutrition and health in the developing world, were driven above all by investments in agricultural S&T that yielded, in strictly economic terms, enormous rates of return; and export-led economic growth, providing the means with which the public and private sectors in many developing countries have contributed to lifting portions of their populations out of poverty, has likewise been driven strongly by technology (*9*).

Relatively simple and inexpensive technologies can have large positive impacts on the most fundamental aspects of well-being, such as public health, as was initially demonstrated in today's industrialized countries when they first introduced simple water-treatment technologies (*8*) and has been shown more recently in developing countries with such simple innovations as oral rehydration therapy for diarrheal diseases, which has sharply lowered death rates even in circumstances where incomes were not rising (*9*). A current example of large "bang for the buck" in the public health domain is the rapid expansion in the use of insecticide-treated bed nets to combat malaria, particularly in Africa, funded by a combination of private, governmental, and multilateral initiatives (*10*).

These insights and examples only serve to underline how much better we could be doing with the application of S&T to meeting basic

1 CONTRIBUTORS TO GLOBAL MORTALITY IN 2000

Fundamental cause	Primary shortfalls and drivers	Millions of years of life lost
Childhood and maternal malnutrition	Poverty, technology, apathy	200
High blood pressure, cholesterol, overweight, low physical activity	Consumption, denial	150
Unsafe sex	Ignorance, denial	80
Tobacco	Denial	50
Unsafe water	Poverty, technology, apathy	50
War and revolution (20th-century average)	Violence	40
Indoor smoke from solid fuels	Poverty. technology	35
Alcohol	Wasted potential, ignorance, denial	30
Urban air pollution	Consumption, technology	6
Global climate change	Consumption, technology, denial	5

Table 1. Contributors to global mortality in 2000, categorized by fundamental causes. Units in column three are millions of years of life lost to premature deaths in the year 2000 (= numbers of premature deaths in 2000 from the indicated cause × average loss of life expectancy per death from that cause). The categorization of fundamental causes and associated lost-life estimates are from WHO (*5*), except for "war and revolution"; that figure is the author's estimate for the 20th-century annual average, based on a UN figure of about 100 million conflict-related deaths in the 20th century (*6*) and the author's guess of 40 years of lost life expectancy per conflict-related death. Attributions of relevant "shortfalls and drivers" are the author's (*7*).

human needs if a more respectable effort were being devoted to this aim. The dimension of the shortfall is suggested by the figures for official development assistance (ODA) from the Organization for Economic Cooperation and Development (OECD): A recent upturn in ODA has brought the total back only to the 1990 level of 0.33% of the gross national income of the donor countries (this despite long-standing international agreement on a target of 1%, which itself seems pathetically small in relation to both the needs and the opportunities) (*11*). The United States, by far the richest country in the world in gross national income, is the stingiest among all the OECD countries in the fraction of it, 0.2%, devoted to ODA. [Americans spend 3.5 times more on tobacco and 20 times more on defense (*12*).]

Land, Water, and Terrestrial Biota

Turning to the environmental dimension of sustainable well-being, a central challenge is how to manage the intensifying competition among human uses for the land, water, and biota of the planet. Those uses fall mainly into three categories:

•Land and water for housing, commerce, industry, and infrastructure (energy, transport, and communications).

•Land, water, and net primary productivity (NPP) for the production of food, feed for domestic animals, fiber, biofuels, and chemical feedstocks.

•Land, water, and biota (plants, animals, and microorganisms) for recreation, beauty, the solace of unspoiled nature, and other "ecosystem services."

The term "ecosystem services" refers to functions of ecosystems that underpin human well-being, including, besides those already separately mentioned, regulation of water flows; detoxification and purification of soil, water, and air; nutrient cycling; soil formation and maintenance; controls on the populations and distribution of pests and pathogens; pollination of flowers and crops; maintenance of biodiversity; and regulation of climate (through, e.g., evapotranspiration, reflectivity, and carbon sequestration) (*13*, *14*).

The competition among these uses for the limited supplies of land and water and the biota that these can support is being intensified by rising population and affluence, with affluence providing a particularly powerful multiplier in the demand for land and water for agriculture and pasture as rising incomes translate into higher consumption of meat. Also contributing to the intensification of the competition is global climate change (about which more will be said below), which is sharply increasing the demand for both biofuels and carbon sequestration in intact forests (*15*) at the same time as it stresses farms and forests in many parts of the world with increased heat, drought, and wildfires (*16*).

A number of other factors complicate the challenge of managing the competing uses of land, water, and biota. One is the rising tide of toxic spillovers from energy supply, industry, and agriculture, which reduce the usability of water and otherwise directly stress managed and unmanaged ecosystems alike (more about this below, too). Another is the prevalence of haphazard, unintegrated, and short-range planning in relation to society's uses of land and water. A third—and one of the primary causes of the preceding two—is the frequent failure to charge a reasonable price (or any price at all) for the use of environmental resources or the degradation of environmental conditions and services.

A quantitative picture of world water supply and demand is presented in Table 3 (*17*). A key point is that only about a quarter of total runoff and recharge is actually available for human use (after uncaptured storm runoff and remote areas are subtracted), and nearly 40% of the globally available amount is already being used. (Irrigated agriculture is by far the largest user, and it is the fastest-growing—driven above all by rising demand for grain to feed to animals and now, in the United States especially, for corn to convert to ethanol.) There is a difference of a factor of 40 in current annual water withdrawals per person between the poorest and richest countries, which bodes ill for future water demand in relation to supply as incomes and populations continue to rise.

The widespread supposition that humans can use all of the "available" runoff is in error, moreover. Enough flow must be left in rivers to meet ecological needs. Taking these ecological flow require-

2 MDG'S, TARGETS, AND PACE OF PROGRESS

Goal	Target	Progress
Eradicate extreme poverty and hunger	Proportion of people living on less than $1 per day to be halved between 1990 and 2015	Target already met in East and Southeast Asia, but other developing regions are behind pace needed to meet it by 2015
Achieve universal primary education	Full course of primary schooling for boys and girls everywhere by 2005	Southern Asia, northern Africa, and Latin America on track to meet target; other developing regions behind
Promote gender equality and empower women	Eliminate gender disparities at all levels of education by 2015	Nearly all developing regions far off pace needed to meet target
Reduce child mortality	Reduce under-5 mortality rate by 2/3 between 1990 and 2015	East and Southeast Asia, northern Africa, and Latin American on track to meet target; other developing regions far behind
Improve maternal health	Reduce maternal mortality rate by 3/4 between 1990 and 2015	East and Southeast Asia, northern Africa, and Latin American on track to meet target; other developing regions behind
Combat HIV/AIDS, malaria, and other diseases	Have halted and begun to reverse spread of HIV/AIDS and incidence of malaria by 2015	No. of people with HIV/AIDS may have stabilized in sub-Saharan Africa; is rising in most other developing regions
Ensure environmental sustainability	Proportion of people lacking access to safe drinking water and basic sanitation to be halved between 1990 and 2015	East and Southeast Asia, northern Africa, and Latin America on track to meet sanitation target; other developing regions behind
Develop a global partnership for development	No quantitative target; a range of qualitative goals address mechanisms of assistance	If official development assistance is the index, progress is slight; debt and trade measures look better

Table 2. MDGs, targets, and pace of progress (*10*, *11*).

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ments into account reveals that many of the world's river basins are already overexploited: Human withdrawals are leaving less water in rivers than needed to meet ecological requirements. Rising human water demands are also leading, at many locations around the world, to the extraction of groundwater from aquifers at rates exceeding natural recharge, leading to declining water tables, wells running dry, and increased drilling and pumping costs (*8*).

The current extent of human exploitation of Eath's land surface and vegetation is, similarly, far greater than is generally supposed. Crops, pastures, and grazing now take up about 40% of the planet's 133 million km^2 of ice-free land (*18*). Forests, which once covered 50 million km^2, have shrunk by about 10 million km^2 in the past 300 years (with half of that loss occurring in the past half century), and desert and near-desert lands have expanded by nearly 10 million km^2. Cities, towns, roads, and airports now cover about 2% of the land area—approaching 3 million km^2 (*18*–*20*).

Arguably a more informative measure of the scale of human intervention in terrestrial ecosystems than areas transformed is the fraction of the NPP of those ecosystems that human activities have eliminated or appropriated for human purposes; a pioneering study in the mid-1980s estimated that humans appropriate about 25% of terrestrial NPP and have eliminated nearly another 15% through land transformations (*21*). Subsequent studies using the more extensive remote-sensing information and geographic information systems (GIS) databases that have become available in the meantime have altered the details of the picture but reinforced the basic finding that, depending on the definitions employed, human activities are appropriating between 25 and 40% of terrestrial NPP (*22*).

Considering the increases in human demands for NPP that are in prospect both for the combination of food and feed and for biofuels, and considering the need to leave large areas of forest substantially intact for purposes of carbon sequestration and other ecosystem functions, these are not encouraging numbers. They become even less so when one considers the loss of biodiversity that has accompanied the level of appropriation of terrestrial NPP already reached.

The Millennium Ecosystem Assessment completed in 2005 developed estimates for contemporary and projected extinction rates compared to past rates suggested by the fossil record: 100 to 1000 times past extinction rates today, another 10 to 100 times higher in the future (*13*). And already in 2000 it was estimated that 18% of mammal species, 12% of bird species, and 8% of plant species worldwide were threatened with extinction (*23*); the projected increases in extinction rates, if they materialize, thus portend a biodiversity catastrophe.

The current state of understanding of ecosystem structure and function does not generally allow prediction of what forms and degrees of local or regional biodiversity decline will lead to severe impacts on basic ecosystem functions and the services associated with them. To confuse this ignorance with cause for complacency would be folly, however. The most elementary common sense (embodied in Aldo Leopold's famous dictum from *A Sand County Almanac* that "The first rule of intelligent tinkering is to save all the parts")—reinforced by a large part of the detailed ecological knowledge accumulated since—tells us that continuing biodiversity loss must eventually exact a large toll in ecosystem performance and resilience against shocks and stresses both natural and anthropogenic (*24*).

What is needed from S&T in relation to the intensifying competition for land, water, and biota? We need, for reasons both purely scientific and as a basis for sensible ecosystem management, a large increase in ecological research focused on the relations linking biodiversity and other aspects of ecosystem condition with ecosystem function and services; and we need a better understanding of what those services do and could deliver in support of human well-being, as well as better ways to quantify their value for incorporation into the market and nonmarket processes shaping the future of ecosystems (*25*).

We need more studies that combine projected land requirements for food and feed, fiber, biofuels, and infrastructure—rather than pretending that each use can be analyzed separately—and that attempt to reconcile the combined demands with the requirement for enough land covered by intact forests and other native ecosystems to provide the carbon sequestration and other ecosystem services society cannot do without (*26*). We need more effective use of the capabilities provided by satellite imagery and other remote sensing, and by GIS, both for conducting such studies and for conveying the results to publics and decision-makers in forms they will understand and use (*27*). And, not least, we need technologies for extracting food, fiber, and fuel from agricultural and forest ecosystems in ways less disruptive of the other services those systems provide than the technologies typically used today (*28*).

3 THE WORLD'S WATER

Stocks		Cubic kilometers
Water in the oceans (~35,000 parts per million salt)		1,400,000,000
Water locked up in ice		30,000,000
Groundwater		10,000,000
Water in lakes and rivers		100,000
Water in the atmosphere		10,000
Flows		**Cubic kilometers per year**
Precipitation on land		120,000
Evaporation from land		70,000
River runoff and groundwater recharge		50,000
Available river flow and recharge		12,000
Withdrawals for human use		5,000
of which	Agriculture 3,500	
	Industry 1,000	
	Domestic 500	
World desalting capacity		13
Flows per capita		**Cubic meters per person per year**
Available river flow and recharge/world population		1,800
Per capita withdrawals, global average		800
Nigeria		50
Israel		300
China		500
Mexico		800
Italy		1,000
United States		2,000
World desalting capacity/world population		2

Table 3. Where is the world's water and where is it going? Compiled and rounded from several sources (*17*). 1 km^3 = 10^9 m^3 = 10^{12} liters = 264 × 10^9 gallons. Available river flow and recharge = runoff + recharge – uncaptured storm runoff – remote areas. Withdrawals for human use are estimated for 2007. Per capita withdrawals are data for 2000.

The Oceans

The oceans cover 70% of the surface of the planet, contain 98% of the water, and contribute about half of the NPP. They are a gigantic bal-

PHOTO CREDITS: (TOP) KARL WEATHERLY/GETTY IMAGES; (BOTTOM LEFT TO RIGHT) DC PRODUCTIONS/GETTY IMAGES; DIGITAL VISION/GETTY IMAGES; GETTY IMAGES

ance wheel in Earth's weather and climate. They are an immense reservoir of biodiversity; one even less cataloged and characterized than that of the terrestrial biota. And fisheries derived from them supply 20% or more of the per capita animal-derived protein consumed by 40% of the human population (*29*).

Although the oceans are perceived by many as being too gigantic and immutable to be much influenced by human activities, they have actually been, like the land, substantially altered by human influences. Human-caused warming of Earth's surface and atmosphere has penetrated the oceans to depths of hundreds of meters; and absorption by the ocean of part of the carbon dioxide (CO_2) added to the atmosphere by human activities has lowered the average pH of seawater by about 0.1 (*30*). Lead and mercury mobilized by humans move through marine food webs, concentrating at the higher levels, as do synthetic organic compounds such as DDT and PCBs. No part of the oceans is free of traces of oil spills or free of plastic trash.

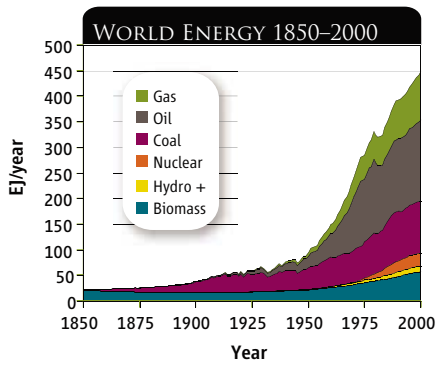

Fig. 1. World supply of primary energy 1850–2000 (*40*). Primary energy refers to energy forms found in nature (such as fuelwood, crude petroleum, and coal), as opposed to secondary forms (such as charcoal, gasoline, and electricity) produced from the primary ones using technology. "Hydro +" includes hydropower, geothermal, wind, and solar. Fossil fuels are counted at higher heating value and hydropower is counted as energy content, not fossil-fuel equivalent. 1 exajoule (EJ) = 10^{18} joules = 0.95 quadrillion Btu.

The most conspicuous of human impacts on the oceans to date has been the decline in the populations of many of the fish and shellfish we harvest for food. Marine fish catches reached a plateau in the mid-1990s and have been maintained there since only by dint of harvesting lower in the food web; continuing expansion of the total supply of protein from fish and shellfish has depended on rapid growth in aquaculture (*31*). The real magnitude of the human impact, however, is revealed only by looking region by region and species by species at the fish and shellfish stocks on which the catch had depended; it is a picture of devastating decline, brought about not only by unsustainable harvest of target species but also by the extensive bycatch and bottom-habitat destruction brought about by widely used if reprehensible fishing techniques (*32*).

Coral reefs, which have the highest density of biodiversity in the oceans, are also increasingly endangered. Originally the risks to reefs came mainly from subsistence fishing and sediment runoff from agriculture and land development on inhabited islands; to this was later added the stress on reef fish populations from rapidly expanding commercial fishing to supply the aquarium trade in North America and Europe and the live-fish restaurant trade in East and Southeast Asia, as well as physical damage to the reefs from the influx of cruise ships and the reef-walking tourists they carry (*33*).

Today, coral reefs are being affected throughout their range by two further factors that are independent of local population densities, tourist influxes, and commercial fishing fleets: increasing water temperatures, which can cause bleaching (ejection of the living coral organisms from the calcium carbonate structure) and disease; and declining pH, which hinders the ability of organisms to make the calcium carbonate. A recent survey concluded that 30% of the world's coral reefs are already severely damaged and that 60% could be lost by 2030 (*33*).

Another sign of trouble in the oceans is the rapid proliferation of harmful algal blooms and the oxygen-depleted "dead zones" that are often the ultimate result. This phenomenon is largely driven by overfertilization of coastal zones by river runoff laden with nutrients from sewage and agriculture. The number of regions affected and the scale of the impact in individual regions appear to have been growing recently, with a doubling time on the order of a decade (*29*, *34*).

Scientifically, technologically, and politically, human pressures on the oceans are even more challenging to deal with than the pressures on terrestrial ecosystems discussed above. Difficulties of observation and study in the oceans mean that the marine realm is less well explored and less well understood than terrestrial ecosystems. Technologically, the oceans are a more difficult operating environment than the land for almost any purpose. Politically, the problems of governance and management of ocean resources and the ocean environment are compounded by the circumstance that most of the world ocean is a commons, not the province of any nation.

Much of what is needed from S&T in relation to the challenge of sustainability for ocean systems and services, however, is similar to what is needed on the terrestrial side: more research on marine ecosystem structure, function, and service; more and better monitoring and reporting, in forms meaningful to and usable by decision-makers; and more integration of analyses relating to multiple interacting uses and stresses, so that limits on what is sustainable can be identified before they are exceeded. Also needed on the marine side is technological change in relation to what we already know is unsustainable: replacement of harvesting technologies that destroy habitat and decimate bycatch with more resource-friendly alternatives, and modification of agricultural and sewage-treatment practices on land in order to drastically reduce the dead zone–inducing impacts of nutrient-laden river runoff (*35*).

The Energy-Economy-Environment Dilemma

The essence of this dilemma resides in two robust propositions (*36*–*38*): First, reliable and affordable energy is essential for meeting basic human needs and fueling economic growth. Second, the harvesting, transport, processing, and conversion of energy using the resources and technologies relied upon today cause a large share of the most difficult and damaging environmental problems society faces.

Contemporary technologies of energy supply are responsible for most indoor and outdoor air pollution exposure, most acid precipitation, most radioactive wastes, much of the hydrocarbon and trace-metal pollution of soil and groundwater, nearly all of the oil added by humans to the oceans, and most of the human-caused emissions of greenhouse gases that are altering the global climate (*39*).

The study of these environmental impacts of energy has been a major preoccupation of mine for nearly four decades. I have concluded from this study that energy is the hardest part of the environment problem; environment is the hardest part of the energy problem; and resolving the energy-economy-environment dilemma is the hardest part of the challenge of sustainable well-being for industrial and developing countries alike.

Figure 1 shows the composition of world primary energy supply during the bulk of the fossil-fuel era to date, from 1850 to 2000 (*40*). Energy use increased 20-fold over this period—that number being the product of a somewhat

greater than fivefold increase in world population and a somewhat less than fourfold increase in average energy use per person (*41*). Fossil-fuel use increased more than 150-fold, rising from 12% of the modest energy use of 1850 to 79% of 2000's much larger total. By 2005, fossil fuels were contributing 81% of the world primary energy supply, 82% in China, and 88% in the United States (*42*); even in the electricity sector (where nuclear, hydropower, wind, solar, and geothermal energies make their largest contributions), fossil fuels accounted for two-thirds of global generation (Table 4).

The huge increase in fossil-fuel use over the past century and a half played a large role in expanding the impact of humankind as a global biogeochemical force (*43*), not only through the associated emissions of CO_2, oxides of sulfur and nitrogen, trace metals, and more, but also through the mobilization of other materials, production of fertilizer, transport of water, and transformations of land that the availability of this energy made possible (*44*). At the end of the 20th century and the beginning of the 21st, the fossil-fuel–dominated energy supply system continued to impose immense environmental burdens at local, regional, and global scales, despite large investments and some success in reducing emissions to air and water per unit of energy supplied (*29*).

Fine particles appear to be the most toxic of the usual air pollutants resulting from the combustion of fossil and biomass fuels, and whether emitted directly or formed in the atmosphere from gaseous precursors, they have proven difficult to control (*45*). The concentrations of fine particulates in urban air in the United States, Western Europe, and Japan have mostly been falling in recent years, but in cities across the developing world the concentrations have risen to shockingly high levels—often several times the WHO guidelines (*29*). As noted above in connection with Table 1, population exposures to particulate matter from the combustion of fossil and biomass fuels indoors are even greater, with commensurate impacts on health.

A major regional impact of fossil-fuel combustion is wet and dry deposition of sulfur and nitrogen, much of it in acidic forms. Of the sulfur oxide and nitrogen oxide emissions that are the precursors of this fallout, the former are somewhat easier to control technologically. Global emissions of both are now increasing, however, as rapid expansion of poorly controlled sources in Asia, and to a lesser extent in Africa and Latin America, is now more than offsetting reductions in the industrialized countries (*29*).

Mid-range projections for energy growth over the next few decades show world use of energy reaching 1.5 and 2 to 2.5 times the 2005 level by 2030 and 2050, respectively; electricity generation in these "business-as-usual" cases nearly doubles by 2030 and triples by 2050 (*46*). Although these are daunting numbers from the standpoint of sustainability, the problem is not that the world is running out of energy. It isn't (*37*, *47*). But it is running out of cheap and easy oil and gas, and it is running out of environmental capacity to absorb, without intolerable consequences, the impacts of mobilizing these quantities of energy in the ways we have been accustomed to doing it (*48*).

Much discussion of the oil issue has been framed around the contentious question of "peak oil" (*49*): When will global production of conventional petroleum reach a peak and begin to decline, as U.S. domestic production did around 1970? The question derives its importance from the proposition that reaching this peak globally will presage large and long-lasting increases in the price of oil, plus a costly and demanding scramble for alternatives to fill the widening gap between the demand for liquid fuel and the supply of conventional petroleum.

Oil-supply pessimists argue that the peak of conventional oil production could occur any time now; oil-supply optimists say it probably won't happen until after 2030, perhaps not until after 2050. Similar arguments go on about conventional supplies of natural gas, the total recoverable resources of which are thought to be not greatly different, in terms of energy content, from those of crude petroleum.

In my judgment, it's difficult to tell at this juncture whether the optimists or the pessimists are closer to right about when the world will experience peak oil, but the answer is not very important as a determinant of what we need to be doing. After all, it's clear that heavy oil dependence carries substantial economic and political risks in a world where high proportions of the reserves and remaining recoverable resources lie in regions that are unstable and/or controlled by authoritarian governments that have sometimes been inclined to wield oil supply as a weapon. It's also clear that world oil use (which is dominated by the transport sector and, within it, by motor vehicles) is a huge producer of conventional air pollutants, as well as being about equal to coal burning as a contributor to the global buildup of the heat-trapping gas CO_2 (*29*, *42*). Given these liabilities, it makes sense to be looking urgently for ways to reduce oil dependence (while working to clean up continuing uses of oil), no matter when we think peak oil might occur under business as usual.

Indeed, the problem of how to reduce the dangers from urban and regional air pollution and from overdependence on oil in the face of rising worldwide demand for personal transportation is one of the two greatest challenges at the energy-economy-environment intersection. The other one is how to provide the affordable energy needed to create and sustain prosperity everywhere without wrecking the global climate with the CO_2 emitted by fossil-fuel burning.

Climate is the envelope within which nearly all other environmental conditions and processes important to human well-being must function (*50*). Climate strongly influences (so climate change directly affects) the availability of water; the productivity of farms, forests, and fisheries; the prevalence of oppressive heat and humidity; the geography of disease; the damages to be expected from storms, floods,

4 WORLD ENERGY SUPPLY IN 2005

		WORLD	USA	CHINA
Primary energy (exajoules)		514	106	80
of which	Oil	34%	40%	18%
	Natural gas	21%	24%	2%
	Coal	26%	25%	62%
	Nuclear energy	6%	8%	0.6%
	Hydropower	2%	1%	2%
	Biomass and other	11%	3%	15%
Primary energy (terawatt-hours)		17,300	4,000	2,400
of which	Coal	40%	50%	80%
	Oil and gas	26%	21%	3%
	Nuclear	16%	20%	2%
	Hydropower	16%	7%	15%
	Wind, geothermal, and solar	2%	2%	0.1%

Table 4. World energy supply in 2005. About a third of the primary energy is devoted to electricity generation. Net electricity = gross generation less the electricity used within the generating facility. In the "primary energy" column, hydropower is counted as energy content, not fossil-fuel equivalent. "Other" includes wind, geothermal, and solar energy (*42*).

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droughts, and wildfires; the property losses to be expected from sea-level rise; the investments of capital, technology, and energy devoted to ameliorating aspects of climate we don't like; and the distribution and abundance of species of all kinds (those we love and those we hate). A sufficient distortion in the climatic envelope, as recent human activities are well on the way to achieving, can be expected to have substantial impacts in most of these dimensions.

Indeed, after a rise in global average surface temperature of about 0.75º ± 0.20ºC since 1880–1900 (*51*), changes in most of these categories, and significant damages in many, have already become apparent (*5*, *10*, *16*, *52*, *53*). Large impacts from seemingly modest changes in global average surface temperature underline the reality that this temperature is a sensitive proxy for the state of the world's climate, which consists of the patterns in space and time not only of temperature and humidity but of sun and clouds, rainfall and snowfall, winds and storm tracks, and more. (The sensitivity of the temperature proxy for the state of the climate is often illustrated by the observation that the difference in global average surface temperature between an ice age and a warm interglacial—drastically different climates—is only about 5ºC.)

There is no longer any serious doubt that most of the climatic change that has been observed over the past few decades has been due to human rather than natural influences (*54*). As shown in Table 5, the largest of the positive human "forcings" (warming influences) has been the buildup of CO_2 in the atmosphere over the past two and a half centuries. (About two-thirds of this buildup has come from fossil-fuel burning and the other one-third from land-use change.) Other important contributors have been methane from energy supply, land-use change, and waste disposal; halocarbons from a variety of commercial and industrial applications; nitrous oxide from fertilizer and combustion; and soot from inefficient engines and biomass burning. Partially offsetting cooling effects have been caused by the reflecting and cloud-forming effects of human-produced particulate matter and by increased surface reflectivity due to deforestation and desertification.

Facing the menace of growing, human-caused disruption of global climate, civilization has only three options: mitigation (taking steps to reduce the pace and the magnitude of the climatic changes we are causing); adaptation (taking steps to reduce the adverse impacts of the changes that occur); and suffering from impacts not averted by either mitigation or adaptation. We are already doing some of each and will do more of all, but what the mix will be depends on choices that society will make going forward. Avoiding increases in suffering that could become catastrophic will require large increases in the efforts devoted to both mitigation and adaptation.

A 2007 report for the UN Commission on Sustainable Development, focused on what to do, emphasizing mitigation and adaptation equally, concluded that the chances of a "tipping point" into unmanageable degrees of climatic change increase steeply once the global average surface temperature exceeds 2º to 2.5ºC above the pre-industrial level, and that mitigation strategies should therefore be designed to avoid increases larger than that (*52*). Having a better-than-even chance of doing this means stabilizing atmospheric concentrations of greenhouse gases and particles at the equivalent of no more than 450 to 500 parts per million by volume (ppmv) of CO_2 (*55*, *56*).

A mitigation strategy sufficient to achieve such stabilization will need to address methane, halocarbons, nitrous oxide, and soot as well as CO_2, but the largest and most difficult reductions from business-as-usual trajectories of future emissions are those needed for CO_2 itself. The difficulty in the case of CO_2 emissions from the energy system resides in the current 80% dependence of world energy supply on fossil fuels, the technical difficulty of avoiding release to the atmosphere of the immense quantities of CO_2 involved, and the long turnover time of the energy-system capital stock (meaning that the shares of the different energy sources are hard to change quickly) (*57*). In the case of the 15 to 25% of global CO_2 emissions still coming from deforestation (essentially all of it now in the tropics), the difficulty is that the causes of this deforestation are deeply embedded in the economics of food, timber, biofuel, trade, and development, and in the lack of valuation and marketization of the services of intact forests (*58*).

Stabilizing atmospheric CO_2 at 500 ppmv would be possible if global emissions from fossil-fuel combustion in 2050 could be cut in half from the mid-range business-as-usual figure of 14 billion metric tons of carbon in CO_2 per year. Numerous studies of how reductions of this general magnitude might be achieved have been undertaken (*59*), and, notwithstanding differences in emphasis, virtually all have shown that: (i) such reductions are possible but very demanding to achieve; (ii) there is no single silver-bullet approach that can do all or even most of the job; (iii) it is essential, in terms of both feasibility of the ultimate aim and cost of achieving it, to begin reductions sooner rather than later; (iv) the quickest and cheapest available reductions will be through improving the efficiency of energy end-use in residential and commercial buildings, manufacturing, and transport, but costlier measures to reduce emissions from the energy supply system will also need to be embraced; and (v) without major

5 DISRUPTING EARTH'S CLIMATE

Cause of forcing	Magnitude of forcing (W/m^2)
Change in atmospheric concentration of	
Carbon dioxide	+1.66 (±0.17)
Methane	+0.55 (±0.07)
Halocarbons	+0.34 (±0.03)
Nitrous oxide	+0.16 (±0.02)
Tropospheric ozone	+0.35 (–0.10,+0.30)
Stratospheric ozone	–0.05 (±0.10)
Soot	+0.3 (±0.2)
Reflecting particles	–0.8 (±0.4)
Cloud-forming effect of particles	–0.7 (–1.1,+0.4)
Change in reflectivity of surface (albedo) due to	
Land-use change	–0.2 (±0.2)
Soot on snow	+0.1 (±0.1)
Change in solar irradiance	+0.12 (–0.06,+0.18)

Table 5. IPCC estimates of principal human-produced and natural forcings since 1750. Forcings are essentially changes in Earth's energy balance, measured in watts per square meter of the planetary surface, with positive values denoting warming influences and negative values denoting cooling. The uncertainty range is given in parentheses. Large volcanic eruptions produce negative forcings of a few years' duration due to the particles they inject into the atmosphere, but they are not included in the table because no trend is evident in the size of this effect over time. Effects of the 11-year sunspot cycle are likewise not shown because they average out over time periods longer than that. Note that the IPCC's best estimate of the contribution of the net change in input from the Sun since 1750 is some 14 times smaller than that of the CO_2 (*30*).

PHOTO CREDITS: (TOP) NASA/GSFC SCIENTIFIC VISUALIZATION STUDIO (SVS); BLUE MARBLE NEXT GENEREATION DATA, RETO STOCKLI; (BOTTOM LEFT TO RIGHT) NASA/GSFC CONCEPTUAL IMAGE LAB.; GISS, NASA; NASA/GSFC AND NASA/JPL SVS

improvements in technology on both the demand side and the supply side—and a major expansion of international cooperation in the development and deployment of these technologies—the world is unlikely to achieve reductions as large as required.

The improved technologies we should be pursuing, for help not only with the energy-climate challenge but also with other aspects of the energy-economy-environment dilemma, are of many kinds: improved batteries for plug-in hybrid vehicles; cheaper photovoltaic cells; improved coal-gasification technologies to make electricity and hydrogen while capturing CO_2; new processes for producing hydrogen from water using solar energy; better means of hydrogen storage; cheaper, more durable, more efficient fuel cells; biofuel options that do not compete with food production or drive deforestation; advanced fission reactors with proliferation-resistant fuel cycles and increased robustness against malfunction and malfeasance; fusion; more attractive and efficient public transportation options; and a range of potential advances in materials science, biotechnology, nanotechnology, information technology, and process engineering that could drastically reduce the energy and resource requirements of manufacturing and food production (*60*).

Also urgently needed from S&T in the energy-climate domain are improved understanding of potential tipping points related to ice-sheet disintegration and carbon release from the heating of northern soils; a greatly expanded research, development, and demonstration effort to determine the best approaches for both geologic and enhanced biologic sequestration of CO_2; a serious program of research to determine whether there are "geoengineering" options (to create global cooling effects that counter the ongoing warming) that make practical sense; and wide-ranging integrated assessments of the options for adaptation (*61*).

Adequately addressing these and other needs in the science and engineering of the energy-environment interaction would probably require a 2- to 10-fold increase in the sum of public and private spending for energy research, development, and demonstration (ERD&D) (*62*). This sounds daunting, but the amounts involved are astonishingly small compared to what society spends for energy itself (*63*). There are signs that the private sector is ramping up its efforts in ERD&D in response to the challenge, but for reasons that have been abundantly documented (*64*), the public sector must also play a large role in the needed expansion. Sadly, until now there has been precious little sign of that happening, notwithstanding abundant rhetoric from political leaders about new technologies being the key to the solution (*65*).

Moving Toward Elimination of Nuclear Weapons

Throughout the Cold War, the world's nuclear arsenals (which reached tens of thousands of nuclear weapons on each side in the USA-USSR confrontation and hundreds each in the possession of the United Kingdom, France, China, and probably Israel) were recognized by nearly everyone as a threat to the existence of a sizable part of the human population and to the well-being of most of it, if any significant fraction of them were ever used. Following the peaceful end of the Cold War at the beginning of the 1990s, however, the salience of the threat from these nuclear weapons rapidly receded in the minds of most people. The most plausible political source of a nuclear conflagration had disappeared, and the only related set of worries that retained any widespread salience was a concern—initially much less compelling and immediate than the Cold War's nuclear threat had been—about the possible acquisition of nuclear weapons by rogue states and terrorists.

The tendency toward complacency about dangers from nuclear weapons in the possession of the major powers was reinforced by considerable shrinkage in the U.S. and Russian arsenals—as weapons now deemed surplus were retired from active service and a process of dismantling was begun—and subsequently by conclusion of the Moscow Treaty of 2002, which appeared to promise further significant cuts. Meanwhile, the refocusing of residual concerns about nuclear weapons on issues of proliferation and terrorism proceeded apace, driven by the initial discovery of a nuclear weapon program in Iraq, the Indian and Pakistani nuclear tests of 1998, the revelation of A. Q. Khan's proliferation network, the unmasking of North Korea's nuclear weapon program, and the exercise of frighteningly organized and destructive (even if non-nuclear) terrorist capabilities on September 11, 2001.

To be concerned about nuclear proliferation and the possibility of nuclear terrorism certainly wasn't and isn't wrong (*66*). But to believe that the nuclear weapons still in the possession of the United States, Russia, and the other de jure nuclear weapon states (*67*) are not themselves still a major threat to the world is to underrate both the direct threat of their use that remains and the ways in which their existence influences the proliferation and terrorism threats.

Concerning the possibility that these major-power weapons might in fact be used, highly relevant facts (which polls show are largely unknown to the U.S. public) are as follows: (i) These arsenals still contain altogether about 20,000 nuclear weapons, of which the United States possesses about half; (ii) most of the U.S. and Russian nuclear weapons are not covered by the Moscow Treaty, which governs only a subcategory called "operationally deployed strategic nuclear weapons" (and which also lacks any provision or mechanism for verification); (iii) the United States and Russia each continue to maintain about 2000 strategic nuclear weapons on short-reaction-time alert, increasing the chance of use by mistake or malfunction; and (iv) the United States and Russia both reserve the "right" of first use of nuclear weapons, including in response to non-nuclear threats. While the chance of large-scale use of U.S. and Soviet/Russian nuclear weapons certainly diminished with the end of the Cold War, then, the danger has by no means completely disappeared (*68*, *69*).

The existing nuclear arsenals and the postures of their owners toward their potential uses and improvement are hardly unconnected, moreover, from the dangers of nuclear proliferation and nuclear terrorism. The evident intentions of the current nuclear weapon states to retain large arsenals indefinitely, to maintain high states of alert, to continue to threaten first use of nuclear weapons even against states that do not possess them, and to pursue development of new types of nuclear weapons for increased effectiveness or new purposes are manifestly incompatible with the bargain embodied in the Non-Proliferation Treaty and corrosive of the nonproliferation regime (*70*).

More specifically, with these stances the nuclear weapon states forfeit any moral authority to which they might aspire on questions of nuclear weapon possession, and they reduce the chances of gaining the cooperation of the world community on technology-transfer restrictions and sanctions directed against proliferators. They also directly encourage proliferation by reinforcing the view that nuclear weapons have great political and military value and by undermining confidence that nonpossession of nuclear weapons means a country need not fear being attacked with them.

Nuclear proliferation itself, when it occurs, tends to increase both the incentives and the opportunities for further proliferation, as well as expanding the opportunities for terrorist acquisition of nuclear weapons. The expansion of opportunities accompanying proliferation

comes not merely because nuclear weapons, nuclear weapons expertise, and nuclear explosive materials have been put in additional hands in additional locations, from which they may spread further (as the Khan network so appallingly demonstrated), but especially because they have been placed into contexts where there has been no experience in controlling them. Constraints on the numbers, dispersion, and contemplated uses of nuclear weapons are important, therefore, both to reduce the probability of accidental, erroneous, unauthorized, or authorized use and to reduce the chances of nuclear weapons coming into the possession of additional proliferant states or terrorists.

Ultimately, however, the only alternative to continued proliferation is achievement of a universal prohibition on nuclear weapons, coupled with means to ensure confidence in compliance. If possession of nuclear weapons does not tend toward zero, it will tend instead toward universality; and though no one can predict the pace of this, it will mean, in the long run, that the probability of use of these weapons will tend toward unity (*71*). There are, moreover, powerful arguments that a prohibition of nuclear weapons is not only a practical and moral but a legal necessity, under international law (*72*). It is also telling that, over the years, more and more of the people who have had command over the U.S. nuclear arsenal and the policies governing its use have reached the conclusion that pursuing prohibition is the only sensible option (*73*).

While the contrary is often claimed, prohibition does not require "un-inventing" nuclear weapons (an impossibility). Societies separately and together have productively prohibited murder, slavery, and chemical and biological weapons without imagining that these have been un-invented. Nor is verification an insurmountable obstacle. Verification, with further innovations both technical and social, can be more effective than most suppose (*74*); and in any case, the dangers to the world from cheating are likely to be smaller than the dangers to be expected in a world from which nuclear weapons have not been banned (*75*).

As for timing, the buildup of the global nuclear weapon stockpile from a dozen in 1946 (all in the possession of the United States) to the peak of about 65,000 in 1986 took just four decades; another two decades later, the number had fallen by more than two-thirds (*76*). I see no reason the world shouldn't aim for getting to zero in another two decades; that is, by about 2025. Crucial early steps in that direction include declarations by the nuclear weapon states that they will never, in any circumstances, use nuclear weapons first or against countries that do not possess such weapons; dealerting of all nuclear forces; a series of progressively deeper cuts in total numbers of nuclear weapons (strategic and nonstrategic, deployed and nondeployed), with physical destruction of all of the weapons made surplus by these cuts and disposition of their nuclear explosive materials in ways that effectively preclude their reuse for weapons, and with internationally agreed means of verification; ratification and entry into force of the Comprehensive Nuclear Test Ban Treaty; and negotiation of a cutoff of production of nuclear explosive materials for weapons (*77*).

S&T can contribute to achieving such progress in several ways: through technical advances that make verifying weapon-reduction agreements easier (and thus make agreeing to them easier); through other technical advances that make nuclear energy technology less likely to be used for nuclear weaponry and/or more likely to be detected if this happens; through applications of science and engineering to the task of reducing the dangers of accidental, erroneous, or unauthorized use of nuclear weapons, as well to the task of obviating any need for nuclear explosive testing of weapons, for as long as these still exist; and through S&T-based integrated assessments clarifying dangers and pitfalls on the path to zero and how to avoid them.

Almost certainly, getting to a world of zero nuclear weapons will be as much a matter of political wisdom, political courage, and diminution in the motivations for armed conflict of any sort as a matter of S&T per se. But in the domain of diminishing motivations for conflict, the alleviation of the other shortfalls in sustainable well-being discussed here—to which, as I have tried to show, S&T have large contributions to make—will be indispensable (*78*).

What Else Is Needed?

Beyond the points made already here about the contributions needed from S&T with respect to the five specific challenges on which I have focused, I want to mention some cross-cutting desiderata. We need:

- A stronger, clearer focus by scientists and technologists on the largest threats to human well-being;
- Greater emphasis on analysis of threats and remedies by teams that are interdisciplinary, intersectoral, international, and intergenerational (as the problems are);
- Undergraduate education and graduate training better matched to these tasks;
- More attention to interactions among threats and to remedies that address multiple threats at once;
- Larger and more coordinated investments in advances in S&T that meet key needs at lower cost with smaller adverse side effects;
- Clearer and more compelling arguments to policy-makers about the threats and the remedies; and
- Increased public S&T literacy.

Most, if not all, of these aims would be advanced by wider acceptance, within the academic scientific and engineering communities and elsewhere, of the proposition that applied, interdisciplinary, and integrative work by individual scientists and technologists and by teams is not necessarily less rigorous, less demanding, or less worthy of recognition—and certainly not less valuable to society—than work that is narrower or "purer" (*79*).

The role of the AAAS in advancing these ideas has been and remains immensely important. It is the largest, most diverse, and most interdisciplinary of U.S. scientific societies, and it is also the most influential. Our flagship publication, *Science*, has the largest paid circulation among all the peer-reviewed science journals in the world and enjoys a well-earned reputation for discerning coverage of the intersection of S&T with public policy (as well as for cutting-edge reports on disciplinary research in multiple fields). The extraordinary intellectual smorgasbord of our annual meeting makes it the year's most important gathering for the growing segment of the S&T community interested in the interactions among S&T disciplines and in the influence of S&T on the human condition. It also draws, appropriately, by far the most and best media coverage of any scientific meeting (*80*).

As a visit to the AAAS Web site at www.aaas.org will reveal, there is much more. A remarkable array of interdisciplinary, intersectoral, practice- and policy-oriented centers, programs, and initiatives operate out of AAAS headquarters and engage the energies of members and the attention of publics and policy-makers all around the world. The AAAS R&D Budget and Policy Program provides the most comprehensive and continuously up-to-date coverage available anywhere on patterns, priorities, and policy underpinnings of U.S. government investments in S&T. Since 1973, the AAAS Science and Technology Policy Fellowship programs have been installing postdoctoral to mid-career scientists and engineers in key venues of the federal government where their insights can inform real-world policy-making

while they learn how the policy process works and how it can be made to work better; there have been something in the range of 2000 of these AAAS S&T fellows, and this tremendous body of talent and experience now constitutes a major part of the national community of teaching and practice in science, technology, and public policy. And the extraordinary AAAS Project 2061 has become a major force in strengthening S&T education in our schools and communities.

What More Can Individuals Do?

Individual scientists and technologists concerned with the roles of S&T in the pursuit of sustainable well-being have available to them an array of avenues and opportunities for effective thought and action. Perhaps the most obvious of these, given what I have just said about the AAAS, is to increase one's support for, participation in, and use of the relevant activities and resources of this organization. The similar activities of other science- and engineering-oriented professional societies, academies, and nongovernmental organizations (NGOs) likewise need and deserve increased participation and support.

More specifically, I would urge every scientist and engineer with an interest in the intersection of S&T with sustainable well-being (in all the senses I have explored here and more) to read more and think more about relevant fields outside your normal area of specialization, as well as about the interconnections of your specialty to these other domains and to the practical problems of improving the human condition; to improve the aspects of your communication skills that are germane to conveying your understandings about these interconnections to members of the public and to policymakers; to actively seek out additional and more effective avenues for doing so (including but not limited to increased participation in the relevant activities of the AAAS and other NGOs); and indeed to "tithe" 10% of your professional time and effort to working in these and other ways to increase the benefits of S&T for the human condition and to decrease the liabilities (*81*).

If so much as a substantial fraction of the world's scientists and engineers resolved to do this much, the acceleration of progress toward sustainable well-being for all of Earth's inhabitants would surprise us all.

References and Notes

1. See especially the classic treatise on sustainable development by the World Commission on Environment and Development, G. H. Brundtland, chair, *Our Common Future* (Oxford Univ. Press, 1987), and the more comprehensive and analytical update by the National Research Council Board on Sustainable Development, *Our Common Journey: A Transition Toward Sustainability* (National Academy Press, Washington, DC, 1999).
2. A number of the formulations in this section are adapted from J. P. Holdren, G. C. Daily, P. R. Ehrlich, in *Defining and Measuring Sustainability The Biogeophysical Foundations,* M. Munasinghe, W. Shearer, Eds. (World Bank, Washington, DC, 1995), pp. 3–17.
3. The quoted formulation is from Robert Kates.
4. This was the key insight in Paul Ehrlich's *The Population Bomb* (Ballantine, New York, 1968), as well as one of those in Harrison Brown's prescient earlier book, *The Challenge of Man's Future* (Viking, New York, 1954). The elementary but discomfiting truth of it may account for the vast amount of ink, paper, and angry energy that has been expended trying in vain to refute it.
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6. UN Development Programme (UNDP), *The Human Development Report 2005: International Cooperation at a Crossroads* (UNDP, New York, 2005).
7. An unsurprising conclusion from Table 1 is that poverty is a bigger cause of loss of life in today's world than high consumption is. More surprising to some, although known to specialists since the early 1980s, is that indoor air pollution from the use of solid fuels in primitive stoves for cooking, boiling water, and space heating in developing countries is a far bigger killer than the outdoor air pollution in all of the world's cities. See K. R. Smith, A. L. Aggarwal, R. M. Dave, *Atmos. Environ.* **17**, 2343 (1983). Also surprising to many is WHO's finding that, already in 2000, climate change was approaching urban air pollution as a contributor to global mortality, principally through the effects of increases in heat waves, floods, droughts, and the incidence of certain tropical diseases. For a discussion of the WHO estimate, arguing that it is conservative, see J. A. Patz *et al., Nature* **438**, 310 (2005).
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11. World Bank, *Global Monitoring Report: Millennium Development Goals* (World Bank, Washington, DC, 2007)
12. See U.S. Dept. of Commerce, *2007 Statistical Abstract of the United States* (U.S. Government Printing Office, Washington DC, 2007). The United States compounds its distinction as the meanest of wealthy countries in aid-giving by claiming the record for the fraction of its aid that is "tied": that is, the money must be used to purchase goods and services from the donor (*6*).
13. Millennium Ecosystem Assessment (MEA), *Ecosystems and Human Well-being: Biodiversity Synthesis* (World Resources Institute, Washington, DC, 2005).
14. G. C. Daily, Ed., *Nature's Services: Societal Dependence on Natural Ecosystems* (Island Press, Washington, DC, 1997).
15. Growing concern about global climate change, which is driven largely by the buildup of CO_2 and other greenhouse gases in the atmosphere, has helped drive increased demand for biofuels because of the impression that they are CO_2-neutral. This is indeed the case if the biomass being used for energy is replaced by new growth as rapidly as it is burned, and if no fossil fuels are used for growing the energy crop, harvesting it, transporting it, and converting it into the desired fuel form. Most often the latter condition is not met in the real world, as it most emphatically is not in the case of corn ethanol, which is by far the most rapidly expanding biofuel enterprise in the United States. But a biofuel operation that is short of CO_2-neutral may still offer some greenhouse gas–abatement benefit compared to direct burning of fossil fuel. See, e.g., A. E. Farrell *et al.*, *Science* **311**, 506 (2006), and J. Hill, E. Nelson, D. Tilman, S. Polasky, D. Tiffany, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 11206 (2006).
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26. See, e.g., B. Soares-Filho *et al.*, *Nature* **440**, 520 (2006).
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49. Credit for the idea of approximating the production trajectory of a depletable resources as a Gaussian curve and for insights about the significance of the peak year and how to predict it belongs to the late geophysicist M. King Hubbert, who in the 1950s used this approach to correctly predict that U.S. domestic production of conventional oil would peak around 1970 [(*36*) and references therein]. He also predicted that world production of crude petroleum would peak between 2000 and 2010. Reviews, extensions, and critiques of Hubbert's approach now constitute a considerable literature; see, e.g., K. Deffeyes, *Hubbert's Peak: The Impending World Oil Shortage* (Farrar, Straus & Giroux, New York, 2002), and C. J. van der Veen, *Eos* **87**, 199 (2006).
50. Some of the formulations about climate in what follows have been adapted from (*48*).
51. The beginning of the buildup of atmospheric greenhouse gases attributable to human activities dates back to even before 1750, the nominal start of the Industrial Revolution and the zero point used by the IPCC for its estimates of subsequent human influences. Earlier human contributions to atmospheric greenhouse gas concentrations came principally from deforestation and other land-use change (*43*). The human influences on global average surface temperature did not become large enough to be clearly discernible against the backdrop of natural variability until the 20th century, however. See especially J. Hansen *et al*., *Proc. Natl. Acad, Sci. U.S.A.* **103**, 14288 (2006), as well as (*16*).
52. P. Raven *et al*., *Confronting Climate Change: Avoiding the Unmanageable and Managing the Unavoidable* (UN Foundation, Washington, DC, 2007).
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54. Even the IPCC, which by its structure and process is designed to be ultraconservative in its pronouncements, rates the probability that most of the observed change has been due to human influences as between 90 and 95% in its 2007 report (*30*).
55. For convenience, the IPCC and other analysts often represent the net effect of all of the human influences on Earth's energy balance as the increased concentration of CO_2 alone that would be needed to achieve the same effect, starting from a reference point of 278 ppmv of CO_2 in 1750. In 2005, when the actual CO_2 concentration was 379 ppmv, the additional warming influences of the non-CO_2 greenhouse gases and soot were the equivalent of another 100 ppmv of CO_2, and the cooling effects of human-produced reflecting and cloud-forming particles and surface reflectivity changes were (coincidentally) equivalent to subtracting about the same amount of CO_2. Thus, the net effect was about what would have been produced by the actual CO_2 increase alone (see Table 5).
56. The relationship between climate forcing (represented as the CO_2 concentration increase that would give the same effect as all of the human influences combined) and the corresponding change in global average surface temperature must be expressed in probabilistic terms because of uncertainty about the value of climate "sensitivity," which is commonly defined as the temperature change that would result from forcing corresponding to a doubling of the 1750 CO_2 concentration. See especially S. Schneider, M. Mastrandrea, *Proc. Natl. Acad, Sci. U.S.A.* **102**, 15728 (2005) as well as (*30*).
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61. D. W. Keith, *Annu. Rev. Energy Environ.* **25**, 245 (2000); P. J. Crutzen, *Clim. Change* **77**, 211 (2006); and (*52*)
62. See, e.g., President's Committee of Advisors on Science and Technology, *Federal Energy Research and Development for the Challenges of the 21st Century* (Executive Office of the President of the United States, Washington, DC, 2007); World Energy Council (WEC), *Energy Technologies for the 21st Century* (WEC, London, 2001); National Commission on Energy Policy (NCEP), *Breaking the Energy Stalemate* (NCEP, Washington, DC, 2004); and G. F. Nemet, D. M. Kammen, *Energy Policy* **35**, 746 (2007).
63. Expenditures of firms and individuals for energy are generally in the range of 5 to 10% of gross domestic product—in round numbers, perhaps a trillion dollars per year currently in the United States and five times that globally. Estimates of expenditures by governments on ERD&D depend on assumptions about exactly what should be included, but by any reasonable definition are currently not more than $12 billion to $15 billion per year worldwide. Private-sector investments in ERD&D are much more difficult to estimate; but, if following the general pattern in the United States they are assumed to be twice government investments, then the public/private total for the world is in the range of $35 billion to $50 billion per year, which is equal to at most 1% of what is spent on energy itself. By contrast, many other high-technology sectors spend 8 to 15% percent of revenues on R&D [see (*62*)].
64. See, e.g., K. S. Gallagher, J. P. Holdren, A. D. Sagar, *Annu. Rev. Environ. Resources* **31**, 193 (2006); President's Committee of Advisors on Science and Technology, *Powerful Partnerships: The Federal Role in International Cooperation on Energy-Technology Innovation* (Executive Office of the President of the United States, Washington, DC, 1999); and (*62*).
65. K. S. Gallagher, A. D. Sagar, D. Segal, P. de Sa, J. P. Holdren, *DOE Budget Authority for Energy Research, Development, and Demonstration Database* (Energy Technology Innovation Project, Cambridge, MA, 2006).
66. National Academy of Sciences, Committee on International Security and Arms Control, *Management and Disposition of Excess Weapons Plutonium* (National Academy Press, Washington, DC, 1994); G. Allison, *Nuclear Terrorism: The Ultimate Preventable Catastrophe* (Henry Holt, New York, 2004); M. Bunn, *Securing the Bomb 2007* (Project on Managing the Atom, Cambridge, MA, and Nuclear Threat Initiative, Washington, DC, 2007).
67. The term "de jure nuclear weapon states" refers to those certified as legitimate albeit temporary possessors of such weapons by the Non-Proliferation Treaty (signed in 1968 and entering into force in 1970), in exchange for their agreement to make progress toward nuclear disarmament (Article VI) and to assist non–nuclear weapon states in acquiring the benefits of peaceful useful energy (Article IV). They are the United States, the Soviet Union (now Russia), the United Kingdom, France, and China.
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69. John P. Holdren, "Beyond the Moscow Treaty," testimony before the Foreign Relations Committee, U.S. Senate, 12 September 2002 (www.belfercenter.org/files/holdren_testimony_9_12_02.pdf).
70. See, e.g., Canberra Commission on the Elimination of Nuclear Weapons, *Report of the Canberra Commission* (Department of Foreign Affairs, Commonwealth of Australia, Canberra, 1996) and (*68*).
71. This was recognized already in the prescient book that Harrison Brown, then a young chemist working in the Manhattan Project, started writing even before the Hiroshima and Nagasaki bombs were exploded: *Must Destruction Be Our Destiny?* (Simon & Schuster, New York, 1946). The Polish/British Manhattan Project scientist Joseph Rotblat also reached this conclusion before World War II ended, left the project as a result, and spent the rest of his 97 years working for the elimination of nuclear weapons (including through the Pugwash Conferences on Science and World Affairs, which he helped organize and lead and with which he shared the 1995 Nobel Peace Prize). See J. Rotblat, *Scientists in the Quest for Peace: A History of the Pugwash Conferences* (MIT Press, Cambridge, MA, 1972); J. Rotblat, in *Les Prix Nobel 1995* (Nobel Foundation, Stockholm, 1996); and J. P. Holdren, *Science* **310**, 633 (2005).
72. International Court of Justice, *Int. Legal Materials* **35**, 830 (1996).
73. G. L. Butler, "Abolition of Nuclear Weapons," speech at the National Press Club, 4 December 1996 (www.wagingpeace.org/articles/1996/12/04_butler_abolition-speech.htm); A. Goodpaster, chair, *An American Legacy: Building a Nuclear-Weapon-Free World* (Stimson Center, Washington, DC, 1997); G. Schultz, H. Kissinger, W. Perry, S. Nunn, *Wall Street Journal*, 6 January 2007, Op-Ed page. General Butler was the commander of all U.S. strategic nuclear forces; General Goodpaster was Supreme Allied Commander in Europe; Schultz, Kissinger, and Perry all served as U.S. secretary of defense.
74. Committee on International Security and Arms Control, National Academy of Sciences, *Monitoring Nuclear Weapons and Nuclear-Explosive Materials* (National Academy Press, Washington, DC, 2005).
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76. Natural Resources Defense Council, *Table of Global Nuclear Stockpiles, 1945–2002*, November 2002 (www.nrdc.org/nuclear/nudb/datab19.asp).
77. See, e.g., (*68–70*, *73*) and National Academy of Sciences, Committee on Technical Issues Related to Ratification of the Comprehensive Nuclear Test Ban Treaty, *Technical Issues Related to Ratification of the Comprehensive Nuclear Test Ban Treaty* (National Academy Press, Washington, DC, 2002).
78. See also J. P. Holdren, "Arms Limitation and Peace Building in the Post–Cold-War World" (Nobel Peace Prize acceptance lecture on behalf of the Pugwash Conferences on Science and World Affairs), *Les Prix Nobel 1995* (Nobel Foundation, Stockholm, Sweden, 1996).
79. A multidecade trend in the right direction is evident in the establishment and success of increasing numbers of interdisciplinary graduate degree programs focused on various dimensions of the science-technology-society intersection in universities of the first rank in the United States and around the world, as well as in the increasing number of prestigious prizes focused on such work and the increasing recognition of its importance by academies of science and engineering through the election of members whose careers have been largely in this domain.
80. This and the subsequent paragraph have been adapted from my candidate statement in the 2004 election for president-elect of the AAAS.
81. Although I have been advocating this tithe for decades, the idea is certainly not original with me. I note here that a similar idea was a major theme in J. Lubchenco's AAAS presidential address in 1997 [*Science* **279**, 491 (1998)].
82. I owe thanks for insight and inspiration to several late mentors (among them Harrison Brown, Roger Revelle, Gilbert White, Jerome Wiesner, Harvey Brooks, and Joseph Rotblat); to other mentors still very much alive (among them Paul Ehrlich, George Woodwell, Richard Garwin, Murray Gell-Mann, and Lewis Branscomb); to previous presidents of the AAAS who have shared my preoccupation with the links between S&T and sustainable well-being (among them Peter Raven, Jane Lubchenco, Shirley Ann Jackson, and Gil Omenn); to my wife (the biologist Cheryl E. Holdren); and to colleagues, students, and friends—too numerous to list here—at all of the institutions where I've worked or visited. I thank the editors of *Science* for their patience and assistance with this essay, and the AAAS staff—above all Alan Leshner and Gretchen Seiler—for their exceptional support throughout my term in the Association's leadership. My work on the topics discussed here has been supported by the John D. and Catherine T. MacArthur Foundation, the William and Flora Hewlett Foundation, the David and Lucile Packard Foundation, the Heinz Family Philanthropies, the Energy Foundation, the Winslow Foundation, the Henry Luce Foundation, and many individual donors to the Woods Hole Research Center. I am most grateful to all of them.

100% Accuracy in Automatic Face Recognition

R. Jenkins* and A. M. Burton

National security and crime prevention often depend on our ability to establish the identities of individuals and check that they are whom they claim to be. This proof of identity is frequently achieved by comparing the individual's appearance to a photo-identification document such as a passport. Although there are now a number of automatic face-recognition devices available, none can cope with the kind of image variability encountered in the real world (*1*). Even in relatively constrained settings performance is far from perfect, and current accuracy levels would translate to thousands of errors in any large-scale system (e.g., transport security). The only system that can reliably cope with real-world image variability is a human observer who is familiar with the faces concerned (*2*). We have recently proposed that human familiarity with a particular face can be modeled by a process of image averaging (*3*), whereby different photos of that face are merged to form a single image (*4*). Here, we show that image averaging can also greatly improve performance of an automatic face-recognition system.

FaceVACS (Cognitec Systems GmbH, Dresden, Germany) (*5*) is an industry standard face-recognition system that has been widely adopted [e.g., SmartGate (Australian Customs Service) at Sydney Airport]. For these studies, we used an online implementation of FaceVACS at the genealogy Web site MyHeritage (My Heritage Limited, Tel Aviv, Israel) (*6*). We had no control over the algorithm used by this system or the database of known faces. The database contained 31,077 photographs of famous faces, comprising an average of nine different photos for each of 3628 celebrities. These photographs were collected from diverse sources and were taken over several decades with various cameras. They are thus highly variable in their quality and cover a wide range of lighting conditions, facial expressions, poses, and age. Users of the Web site upload their own face images, and the system returns the closest matching photograph from its database.

We fed this system photographs from our own famous face database (*5*) in order to assess its accuracy on images of real-world variability. When the identity of the returned photograph matched that of the uploaded image, we recorded a hit. Otherwise, we recorded a miss. Our probe database consisted of 500 images, comprising 20 different photographs for each of 25 male celebrities who were also in the online database. Forty-one of the probe images were identical to images in the online database, and these were excluded from the analysis. The overall hit rate for the remaining 459 different images was 54%. The hit rate for individual faces varied according to the number of images of that face that were in the online database. Performance ranged from 16% correct when seven images were stored to 89% correct when 28 were stored. We next sought to establish whether image averaging could improve overall performance. For each test identity, we created a new image by averaging together the 20 images of that person in our probe database (Fig. 1). Note that the online database and the matching algorithm remained the same; the only change from the first study was that we merged the probe images to create an average image for each face (fig. S1). Surprisingly, this simple process raised the hit rate from 54% to 100%. This is unprecedented for such varied images.

It is possible that the averages were well recognized simply because they incorporated some recognizable photos. To rule out this possibility, we constructed a new set of averages using only those photographs that were unrecognized in the first study. That is, we fixed baseline performance at 0%, so that any improvement above 0% could be attributed solely to the averaging process. Applying image averaging to these missed items raised the hit rate from 0% to 80%.

Our findings show that the simple process of image averaging can dramatically boost automatic face recognition. We demonstrated this improvement with a commercially available algorithm and an online face database over which we had no control. We suggest that image averaging enhances performance by stabilizing the face image. With standard photographs, the match tends to be dominated by aspects of the image that are not diagnostic of identity (e.g., lighting and pose). Averaging together multiple photographs of the same person dilutes these transients while preserving aspects of the image that are consistent across photos. The resulting images capture the visual essence of an individual's face and elevate machine performance to the standard of familiar face recognition in humans. It would be technically straightforward to incorporate an average image into identification documents. Doing so would greatly reduce the incidence of face-recognition errors and raise the prospect of a viable automatic face-recognition infrastructure.

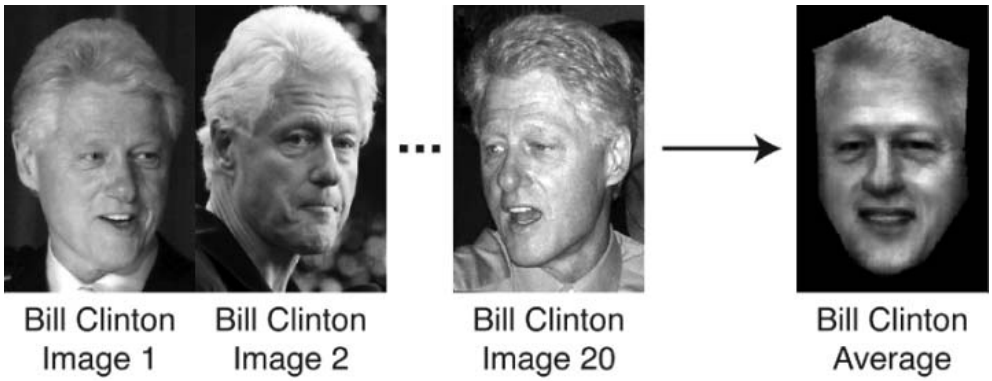

Fig. 1. Example photographs of Bill Clinton and their average (**right**). [Image 1, photo by Marc Nozell (www.flickr.com/photos/marcn/534512066); image 2, photo by Roger Goun (www.flickr.com/photos/sskennel/829574139); image 20, photo by Nelson Pavlosky (www.flickr.com/photos/skyfaller/26752190). All photos were used under a Creative Commons license.] Different pictures of a single face can vary enormously, making automatic recognition difficult. Averaging together multiple photos of the same face stabilizes the image, improving performance dramatically.

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5. Materials and methods are available on *Science* Online.
6. www.myheritage.com
7. We thank G. Cohen at MyHeritage for information about their database. This research was funded by the Economic and Social Research Council, UK.

Supporting Online Material

www.sciencemag.org/cgi/content/full/319/5862/435/DC1
Materials and Methods
Fig. S1
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Probing the Carrier Capture Rate of a Single Quantum Level

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The performance of many semiconductor quantum-based structures is governed by the dynamics of charge carriers between a localized state and a band of electronic states. Using scanning tunneling spectroscopy, we studied the transport of inelastic tunneling electrons through a prototypical localized state: an isolated dangling-bond state on a Si(111) surface. From the saturation of the current at an energy resonant with this state, the hole capture rate by the dangling bond was determined. By further mapping the spatial extension of its wave function, the localized nature of the level was found to be consistent with the small magnitude of its cross section. This approach illustrates how the microscopic environment of a single defect critically affects its carrier dynamics.

A localized state in the band gap of a semiconductor is known to exchange carriers by the emission or capture of electrons/holes with conduction or valence bands, respectively. Because of the limited scale in the size of materials used in nanotechnology, such as quantum dots, nanocrystallites, and nanowires, developments in semiconductor devices critically depend on the ability to probe and understand the carrier dynamics between confined electronic states and the states in the bands of the semiconductor materials (*1*–*3*). So far, a common approach to study the probability (per unit of time) of carrier capture and emission has relied on the use of junction space-charge techniques, such as photocurrent and capacitance techniques (*4*). These techniques were first applied to point defects and interface states, which are generally referred to as "deep level" because the position of the energy level is far apart from both band edges (*5*, *6*). But such techniques require the formation of a space-charge region, which is not always compatible with the current dimensions of single nanostructures. As a result of the size of the space-charge regions, junction techniques also inherently involve the integration of data over a large set of energy levels. Therefore, probing the carrier dynamics of a single deep level is still a challenge.

We report on the use of scanning tunneling microscopy (STM) to probe the hole capture rate of single deep levels with atomic-scale resolution. By saturating the injection of inelastic electrons into the deep level of a Si adatom in the boron-doped Si(111) ($\sqrt{3} \times \sqrt{3}$)R30° surface, we are able to measure the hole capture rate of a Si dangling-bond state and estimate its capture cross section. Its magnitude is found to be consistent with the localization of the deep-level wave function, obtained from the spatial mapping of the differential conductance. Furthermore, by probing a large set of dangling bonds, significant variations in the capture rates are observed and related to the position of the B dopants below the surface. Such a result demonstrates the importance of the potential fluctuations induced by the random distribution of charged impurities on the carrier capture rate of single quantum levels.

The experiments were carried out on a boron-doped Si(111) surface with a scanning tunneling microscope working at 77 K. As a result of the segregation of B atoms during the surface preparation at temperatures higher than 900°C, B impurities substitute for most Si atoms located just under the Si adatom position, causing the passivation of the adatom dangling-bond states (*7*). However, for a few minority sites, the substitution does not take place, leaving their dangling-bond states localized in the band gap region of Si. Such an adatom appears bright in the empty-state STM image (Fig. 1A) (corresponding to a positive sample voltage), in contrast to the darker passivated adatoms (*8*). Performing spectroscopic measurements on a bright adatom with tunneling current setpoints lower than 10 nA reveals a negative differential resistance (NDR) on the current-voltage [$I(V)$] curve (Fig. 1C) and a broad peak on the $dI(V)/dV$ curve (Fig. 1D) in the Si band gap region, which is a signature of the tunneling of electrons through a localized state (*9*). Unexpectedly, with increasing tunneling current setpoints, the NDR peak intensity becomes saturated at 15 nA.

It was recently shown that the transport through this nonresonant dangling-bond state requires two processes (Fig. 1B): a tunneling of an electron between a tip state and the localized state at the energy E_0, and the nonradiative recombination process of the electron with a hole from the valence band (*8*). This second process is assisted by the mechanical vibration of the adatom, and it is the contribution of vibronic states to the current that causes the significant broadening of the NDR peak (*10*). In the steady-state regime, the current corresponding to the tunneling rate W must be equal to the current due to the hole capture rate $c_p p$ by the Si dangling-bond state, thus yielding $I = -\frac{ec_p pW}{c_p p + W}$, where e is the magnitude of the electronic charge, c_p is the hole capture coefficient of the dangling bond, and p is the hole concentration (*11*).

When the tunneling rate is much lower than the capture rate (i.e., the tip-sample distance Z is large, corresponding to small current setpoints),

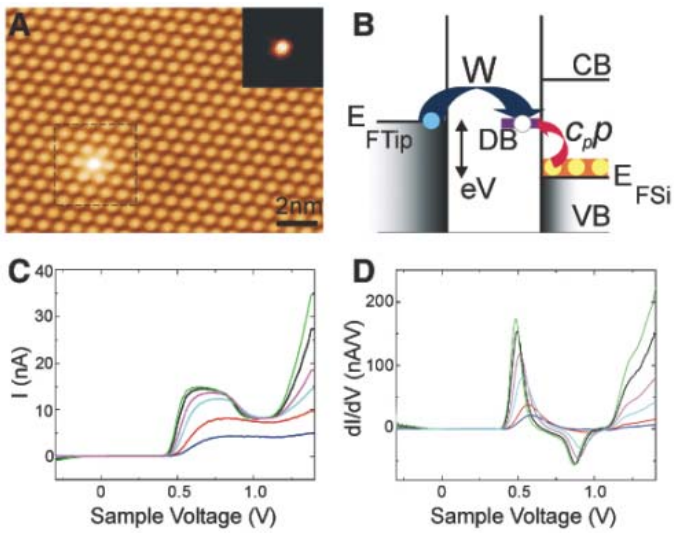

Fig. 1. Saturation of the tunneling current through a single nonresonant dangling-bond state. (**A**) STM image of the boron-doped Si(111) ($\sqrt{3} \times \sqrt{3}$)R30° surface, showing a single nonpassivated bright Si adatom (tunneling setpoint V_S = +1.4 V; I = 1 nA; temperature T = 77 K). The inset shows a differential conductance image recorded at V_S = +0.6 V from inside the dashed square of the topographic image (V_{mod} = 15 mV; f_{mod} = 2 kHz). (**B**) Schematic illustrating the transport through a dangling-bond state (DB) at the energy eV, with a tunneling rate W for the tip electron and a capture rate $c_p p$ for the valence band (VB) hole. E_{FTip} and E_{FSi} denote the tip and Si Fermi levels, and CB denotes the conduction band. (**C**) Tunneling current spectra measured on a nonpassivated Si adatom for different setpoint currents at V_S = +1.4 V. (**D**) Corresponding differential conductance spectra measured with a lock-in amplifier (V_{mod} = 15 mV; f_{mod} = 2 kHz).

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the tunneling current is proportional to the tunneling rate. But, when the tunneling rate increases (higher current setpoints) and becomes higher than the capture rate, the capture rate limits the current driven through the dangling-bond state ($I = -ec_p p$). As a result, the current becomes nearly saturated at the energy where the tip Fermi level is resonant with the dangling-bond state.

Because a precise determination of the saturation current intensity requires increasingly higher tunneling current setpoints, which can sometimes lead to a modification of the surface, we have adopted another approach to directly measure the capture rate. By recording $I(Z)$ curves in the band gap region up to the bottom of the conduction band, we observe (Fig. 2) that the variation of the current intensity deviates from a characteristic exponential increase (*12*–*14*), with the exception of the $I(Z)$ curves acquired with voltages higher than +1.2 V. For these voltages, an exponential increase is seen after an initial plateau and corresponds to the contribution of conduction band states to the tunneling current, resulting from a stronger downward band bending when the tip comes closer to the surface (*15*). But, at lower voltages, the downward band bending is not strong enough, and transport occurs only through the vibronic states of the Si dangling bond down to +0.5 V. For these voltages, the current reaches a maximum value, confirming the saturation observed in Fig. 1A. The highest current intensity of 15 nA is found for a voltage of +0.6 eV, thus yielding a hole capture rate for the dangling-bond state of $c_p p = 10^{11}$ s^{-1}.

From the degenerate concentration of B dopants (10^{20} B·cm^{-3}) in the sample (*8*), we can estimate c_p and find a value of 10^{-9} cm^3 s^{-1}. Although the capture coefficient is the meaningful physical quantity, it is common to introduce the capture cross section $\sigma_p = c_p/\nu_{th}$ (with ν_{th} being the average thermal velocity of the trapped carrier) to characterize the carrier trapping efficiency of a deep level (*2*). A cross section of 1.1×10^{-16} cm^2 is thus obtained and agrees with the theoretical prediction for the capture cross section of a dangling bond in Si (*16*). Such a value also belongs to the order of magnitude usually found experimentally for the capture cross sections of deep levels in semiconductors (*17*), like the so-called P_b center, which consists of a dangling bond located at the Si(111)-SiO_2 interface and where σ_p was measured by deep-level transient spectroscopy (DLTS) (*18*).

Because σ_p is related to the spatial extent of the deep level when the level crosses the valence band to capture a hole while the lattice vibrates (*17*), it is interesting to spatially resolve the square of the deep-level wave function to compare its extent with σ_p. From the spatial mapping of the wave function in the *dI*/*dV* image recorded at the energy of the dangling-bond state (Fig. 1A, inset), we measure an average spatial extent of 10 Å. Assuming that the dangling bond can be modeled by a square well potential with spherical symmetry, resulting from the position of E_0 = 0.4 eV far above the top of the valence band, the radius of the bound state is given by $a = \sqrt{\hbar^2/2m^*E_0}$, where $\hbar$ is Planck's constant h divided by 2π. Taking $m^* = 0.36\ m_O$ (where m_O is the free-electron mass, 9.1×10^{-31} kg), we find a spatial extent of $2a$ = 10.2 Å, which is in good agreement with the experimental value, thus indicating a strong localization of the state, which is as expected from the small magnitude of σ_p.

In contrast to the DLTS technique, which yields an average capture rate for all the deep levels of a space-charge region, STM can readily

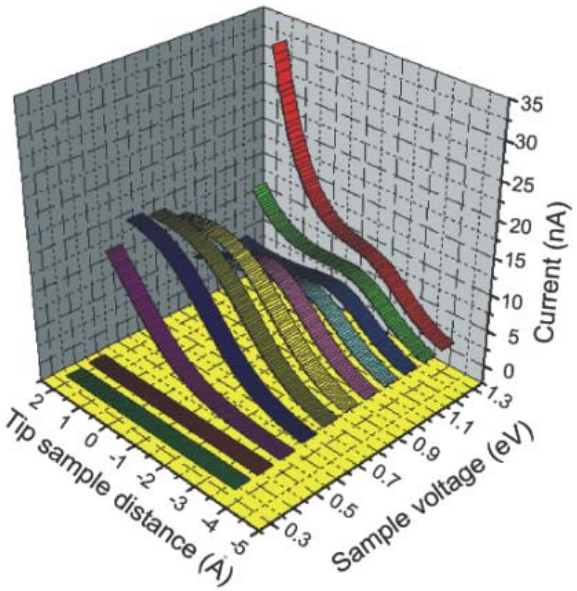

Fig. 2. Tunneling current I_T versus tip displacement at different V_S. The feedback loop (V_S = +1.5 V; I_T = 5 nA) was first opened; V_S was set to a voltage between +1.3 and +0.3 V; and the tip was displaced away from the surface by 3.7 Å, then moved back and forth by 6.0 Å (corresponding to the data shown), and finally returned to its initial position.

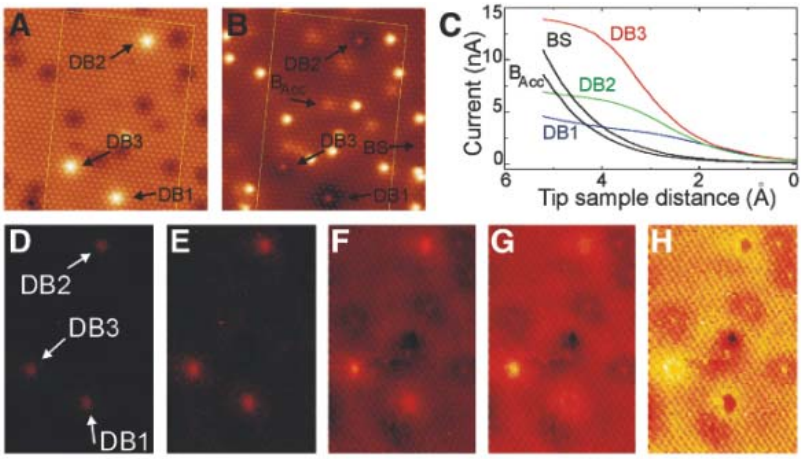

Fig. 3. Variation in the saturation current for three nonpassivated bright Si adatoms labeled DB1, DB2, and DB3. (**A**) Empty-state STM image (V_S = +1.4 V; I_T = 1 nA). (**B**) Filled-state STM image (V_S = –0.3 V; I_T = 1 nA), where a faint protrusion related to a passivated Si adatom located above a subsurface acceptor (B_{Acc}) is indicated, as well as a passivated adatom of the bare surface (BS) that is away from any defects or subsurface dopant atoms. (**C**) Tunneling current versus tip displacement for the three bright Si adatoms, BS, and B_{Acc} at V_S = +1.2 V. (**D** to **H**) Spatial maps of the tunneling current versus tip displacement for distances of 1.07, 1.89, 3.05, 3.86, and 5.17 Å, respectively, at V_S = +1.2 V (feedback parameters V_S = +1.4 V; I_T = 1 nA).

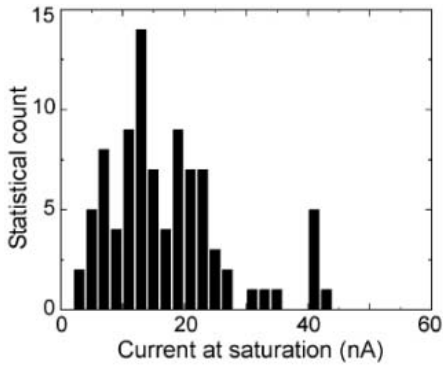

Fig. 4. Distribution of the current intensity at saturation.

probe individual deep levels. As shown in Fig. 3A, three bright adatoms are visible. By performing spatial mapping of $I(Z)$ curves, we observe that the current intensity does not vary in the same manner for these three dangling bonds, as seen in the sequence of Fig. 3, D to H, corresponding to current intensity maps obtained at different tip-surface distances. For the dangling bonds labeled DB1 and DB2, their contrast begins to saturate after the tip has moved toward the surface by 3.05 Å (Fig. 3F) and 3.86 Å (Fig. 3G), respectively, whereas a halo, a sign of saturation, is seen at a higher tip displacement for dangling bond DB3 (Fig. 3H).

The saturation of the current intensity for the three dangling bonds is obtained from the plot of the $I(Z)$ curves in Fig. 3C. We find that the current intensity at saturation is four times higher on DB1 than on DB3. Although the spatial mapping of the $I(Z)$ curves cannot be recorded at the energy E_0 (*19*), similar variations are found when single $I(Z)$ spectra are measured on different dangling bonds at the energy E_0, as illustrated in fig. S1 (*20*). Thus, such a result indicates that the capture rate depends on the environment of the dangling bond.

To understand such variations of the capture rate, we acquired the image in Fig. 3B simultaneously with that in Fig. 3A. In this filled-state image, the three dangling bonds appear bright, but they are each surrounded by a dark region, with different spatial extents and depths. These regions are the signature of the Coulomb interaction between the charged dangling bonds and the free holes. The strength of this interaction is intimately related to the distribution of subsurface charged acceptors. As shown in (*8*), the acceptors appear as bright protrusions superimposed to the atomic corrugation of the Si adatoms in the filled-state STM image (Fig. 3B). Notably, two acceptors are found to be quite close from DB3, whereas no acceptor is visible around DB1. Such a distribution is quite consistent with the variation of the saturated current measured between the three dangling bonds and demonstrates that the potential fluctuations caused by the random distribution of B dopant atoms dramatically change the capture rate of a dangling bond.

By measuring similar $I(Z)$ curves for more than 90 dangling bonds, we found a distribution of the current intensities at saturation that is centered at 16 nA with a SD of 9 nA (Fig. 4). To explain this deviation, we analyzed the $I(Z)$ curves that were measured away from the bright Si adatoms. From the exponential tunneling behavior of these $I(Z)$ curves (see curves labeled BS and B_{Acc} in Fig. 3C), the spatial variations of the apparent barrier height are extracted (*21*) and yield a potential fluctuation range of 25 meV. Such fluctuations are expected to affect both the capture coefficient and the hole concentration. At 77 K, the capture cross section has a thermally activated behavior (*22*), and we estimate that the potential fluctuations induce a variation of the capture cross section by a factor of 1.4 (at most). Furthermore, the heavy doping of the Si sample yields a narrowing of the band gap of 130 meV. The potential fluctuations lead to a modification of the band gap narrowing, causing substantial variations of the hole concentration, which we estimate to range between 0.6×10^{20} and 1.7×10^{20} hole·cm^{-3} (*23*, *24*). Such variations of the capture cross section and hole concentration agree well with the measured distribution of the current intensities at saturation.

Although the capture rate is measured for a nonradiative recombination process involving the emission of vibrations, this new method is expected to be valid for the direct measurements of a wide range of carrier dynamic processes between a bound state and a continuum of states. It should be suitable to explore the capture and relaxation of charge carriers by the bound states of quantum dots or by point-defect states in nanostructures, such as nanowires, nanotubes, and single atomic sheets.

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19. Because there is no state in the band gap region when the tip is above the passivated adatoms, closing the feedback loop between two $I(Z)$ spectra leads to a tip crash for sample voltages below +1 V.
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Spin Conservation Accounts for Aluminum Cluster Anion Reactivity Pattern with O_2

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The reactivity pattern of small (~10 to 20 atoms) anionic aluminum clusters with oxygen has posed a long-standing puzzle. Those clusters with an odd number of atoms tend to react much more slowly than their even-numbered counterparts. We used Fourier transform ion cyclotron resonance mass spectrometry to show that spin conservation straightforwardly accounts for this trend. The reaction rate of odd-numbered clusters increased appreciably when singlet oxygen was used in place of ground-state (triplet) oxygen. Conversely, monohydride clusters Al_nH^-, in which addition of the hydrogen atom shifts the spin state by converting formerly open-shell structures to closed-shell ones (and vice versa), exhibited an opposing trend: The odd-*n* hydride clusters reacted more rapidly with triplet oxygen. These findings are supported by theoretical simulations and highlight the general importance of spin selection rules in mediating cluster reactivity.

Metal-atom clusters occupy a broad middle ground between small molecules and extended solids. Early mass spectrometric studies revealed certain atomic compositions that exhibited unusual stability and were therefore termed "magic." A framework analogous to the atomic shell-filling model has been successful in rationalizing many of these observations on the basis of electronic structure considerations; i.e., the valence electrons are governed by an average potential created by the residual positive charges. The result is a jellium-

like shell structure with "magic" electron numbers 2, 8, 20, 40, 70, etc. (*1*, *2*). Though these "magic" numbers were first recognized for metal clusters of sodium (*3*) and other metals containing s-valence electrons (e.g., Cu, Ag, Au), they have also been applied to Al clusters because there is an overlap of 3s and 3p orbitals for clusters containing more than nine atoms (*4*, *5*). Although the unusual stability of, e.g., Al_{13}^- with its 40 electrons has been well explained (*6*), for Al clusters in general, certain reactivity patterns remain puzzling. One of these is the odd/even effect whereby Al_n^- clusters with an odd number of Al atoms react much more slowly with oxygen than do even-numbered clusters (*7*–*9*). According to previous studies, the reactivity of large Al clusters with oxygen should be determined by two factors, namely, the energy required to remove an Al atom and the electron affinity of the cluster (*10*). However, these factors alone may not be sufficient to describe the observed odd/even effect. The reduced reactivity of the Al_{odd} clusters with triplet oxygen ($^3O_2$) was mentioned frequently in the literature (*11*), but to our knowledge, the role of the spin has not been considered in this context (*7*–*9*). Spin conservation was estimated to be negligible because for multielectron systems like clusters, intersystem crossing processes were expected to take place quickly so that the intermediate products should always have the lowest possible spin multiplicities. Here, we demonstrate that this concept should be reconsidered. Spin conservation has an essential influence not only on reactions of small molecules—textbook examples are the fast reaction of NO radical with O_2 and the low reaction rate between SO_2 and O_2—but also on Al clusters. Similar conclusions have been reached in a recent study on the reactions of several $Al_4H_n^-$ species with O_2 (*12*). To investigate this issue in more detail, we studied reactions between Al_nH^- clusters and triplet O_2 as well as those of mass-selected Al_{13}^- clusters with singlet O_2 by Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS) and by quantum chemical calculations.

Our apparatus and cluster ion source have been described elsewhere (*13*, *14*). The experiments were performed under ultrahigh-vacuum (UHV) conditions, so that only a few collisions with other molecules (approximately one collision per 10 s per cluster) could occur (*13*, *14*). The reaction time can be expanded and primary steps followed. In this way, snapshots of the reaction processes are taken, i.e., cluster degradation due to the formation of molecular aluminum monoxide. Al_2O is known to be a prominent gas-phase species produced in high-temperature reactions of aluminum and oxygen (*15*).

By 1989, Castleman (*16*) and Jarrold (*7*) and their colleagues had respectively demonstrated that anionic and cationic Al cluster ions showed the above-mentioned odd/even effect in the presence of O_2. Hettich (*9*) confirmed this behavior for Al_n^- cluster ions through FT-ICR MS experiments (fig. S1). Motivated by these results, we examined this odd/even effect by exposing mass-selected Al_{13}^- and Al_{14}^- clusters, two representatives of the Al_{odd}^- and Al_{even}^- series, respectively, to an O_2 atmosphere at 10^{-8} mbar. Al_{13}^- clusters proved relatively inert (just as Castleman had reported), and only small traces of Al_9^- clusters (as reaction products) were detected during our FT-ICR MS investigations (Eq. 1).

$$^1Al_{13}^- + {}^3O_2 \rightarrow {}^3[Al_{13}\cdot O_2]^- \quad -0.36\ \text{eV} \quad (1a)$$

$$^3[Al_{13}\cdot O_2]^- \rightleftarrows {}^1Al_{13}O_2^- \quad \text{spin transition} \quad (1b)$$

$$^1Al_{13}O_2^- \rightarrow {}^1Al_9^- + 2\ {}^1Al_2O \quad (1c)$$

$$Al_{13}^-(g) + {}^3O_2 \rightarrow Al_9^-(g) + 2\ Al_2O(g) \quad (\mathbf{1})$$

$$^2Al_{14}^- + {}^3O_2 \rightarrow {}^2[Al_{14}\cdot O_2]^- \quad -2.76\ \text{eV} \quad (2a)$$

$$^2[Al_{14}\cdot O_2]^- \rightleftarrows {}^2Al_{14}O_2^- \quad (2b)$$

$$^2Al_{14}O_2^- \rightarrow {}^2Al_{10}^- + 2\ Al_2O \quad (2c)$$

$$Al_{14}^-(g) + {}^3O_2 \rightarrow Al_{10}^-(g) + 2\ Al_2O(g) \quad (\mathbf{2})$$

In contrast, we found that mass-selected Al_{14}^- clusters reacted spontaneously to give Al_{10}^- [and two Al_2O (*15*, *17*, *18*) equivalents] under the same conditions (Eq. 2).

Although Al_{13}^- is a "double magic" cluster (40 electrons fulfill the shell model and the topology represents a centered icosahedron) (*19*), and thus of particular importance, analogous findings were also found for reactions of other odd- and even-numbered clusters with O_2. Generally, all Al_{odd}^- clusters react much more slowly with triplet oxygen than do Al_{even}^- clusters.

To understand the experimental observations, we drafted the following spin conservation hypothesis. With its 40 valence electrons (closed shell), the spin multiplicity of the ground state of the Al_{13}^- cluster is a singlet (^1A_g) and is labeled by $^1Al_{13}^-$ in the text below. Correspondingly, $^2Al_{14}^-$ has a doublet ground state ($^2A''$) due to its one unpaired electron [detailed information on quantum chemical calculations and spin states is available in the supporting online material (fig. S3 and table S1)]. Initially, these species form adducts with $^3O_2$ with the associated oxygen molecule bound to the surface of the cluster (denoted by $[Al_{13}\cdot O_2]^-$ and $[Al_{14}\cdot O_2]^-$ in Eqs. 1a and 2a, respectively). Due to spin conservation restrictions (*20*), $^3[Al_{13}\cdot O_2]^-$ is formed in a triplet state and $^2[Al_{14}\cdot O_2]^-$ in a doublet state. Subsequently, the oxygen molecule dissociates on the surface of the structurally rearranging cluster (Eqs. 1b and 2b, respectively), causing the cluster to heat up and leading to fragmentation of the cluster (Eqs. 1c and 2c). Because $^3[Al_{13}\cdot O_2]^-$ is in a triplet state, whereas its energetically accessible fragments, Al_9^- and Al_2O, are all singlets, there must be a spin transition—an inherently slow process. The direct formation of $^1[Al_{13}\cdot O_2]^-$ (singlet state) from $^1Al_{13}^-$ and $^3O_2$ is spin forbidden and therefore unlikely to proceed, because spin-orbit coupling in the case of light metals like alumi-

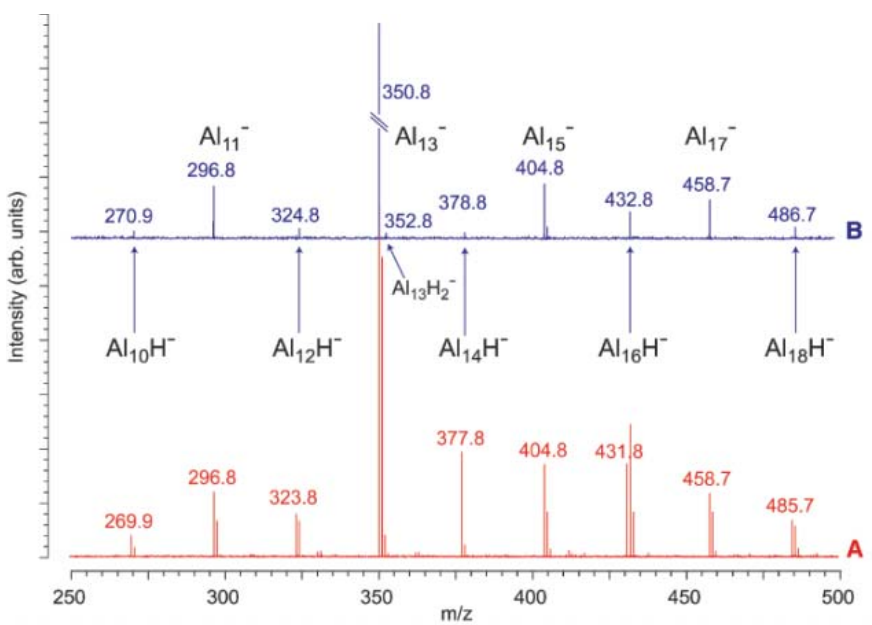

Fig. 1. Typical FT-ICR mass spectra after laser-desorption/ionization. (**A**) In the presence of H_2 as the collision gas during the cluster generation, $Al_nH_m^-$ clusters are formed. (**B**) After admitting $^3O_2$, all $Al_{odd}H^-$ react rapidly away. *m/z*, mass/charge ratio.

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num is small, preventing appreciable overlap between the potential energy surfaces (PESs) of different spin states (*20*). In contrast, in the case of Al_{14}^-, no such spin transition need occur because the initially formed $^2[Al_{14}{\cdot}O_2]^-$ can react directly via $^2Al_{14}O_2^-$ to form products $^2Al_{10}^-$ and Al_2O. We therefore hypothesized that for reactions of Al clusters with $^3O_2$, diminished rates are expected if the initially formed O_2 adduct is a triplet (due to spin conservation, e.g., $^3[Al_{13}{\cdot}O_2]^-$) and the final products are singlets (here, $^1Al_9^-$ and $^1Al_2O$).

To substantiate this idea experimentally, we manipulated the spin state of the aluminum-containing reactants by preparing aluminum hydride cluster anions, Al_nH^-, and exposed them to $^3O_2$; we changed the spin of O_2 by generating singlet oxygen ($^1O_2$), allowing it to react with Al_{13}^- and other odd-numbered Al_n^- clusters.

Upon addition of a hydrogen atom, the number of electrons in the cluster core changes by one, which also changes the spin state. We generated Al_nH^- clusters by reaction of Al_n^- clusters with hydrogen (Fig. 1A) (*21*). All $Al_{odd}H^-$ reacted rapidly with $^3O_2$, whereas $Al_{even}H^-$ proved inert. Thus, the reactivity pattern was notably inverted relative to Al_n^- behavior, e.g., $Al_{13}H^-$ reacted, even though Al_{13}^- (and $Al_{13}H_2^-$) had been nearly unreactive (Fig. 1B), whereas the initial $Al_{14}H^-$ signal remained unchanged, while Al_{14}^- reacted away (Eqs. 3 and 4). The observed universality of such behavior for these systems indicates that triplet oxygen reacts rapidly with all species in a doublet spin state (and possibly higher spin states), whereas it reacts much more slowly with species in a singlet state. The shell model considerations play a role as well by explaining the particularly unreactive character of certain clusters, most notably Al_{13}^-.

$$^2Al_{13}H^-(g) + {}^3O_2 \rightarrow {}^2[HAl_{13}{\cdot}O_2]^- \quad -1.93\ \text{eV} \quad (3a)$$

$$^2Al_{13}H^-(g) + {}^3O_2 \rightarrow {}^2Al_9H^-(g) + 2\ Al_2O(g) \quad (\mathbf{3})$$

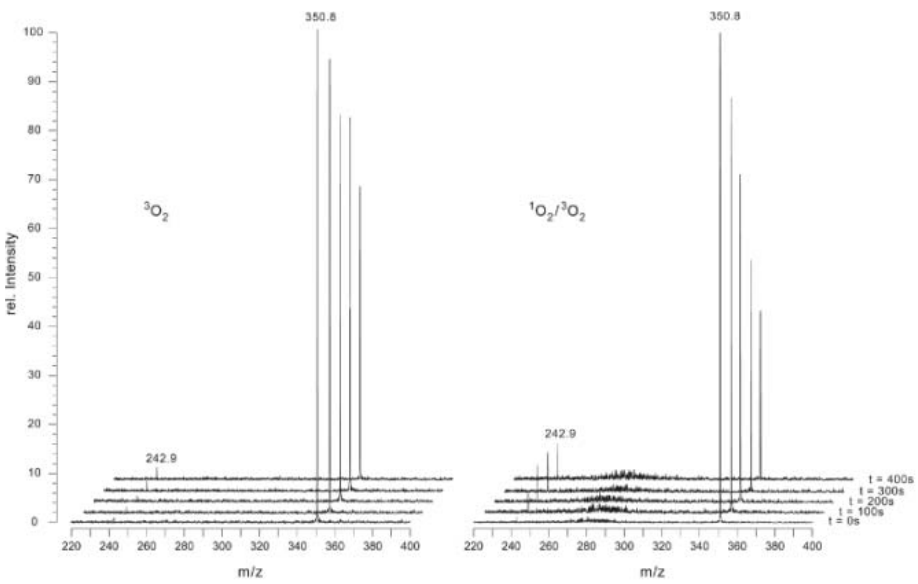

Fig. 2. Reactions of mass-selected Al_{13}^- clusters with $^3O_2$ (**left**) and with a $^1O_2/^3O_2$ mixture (**right**). The FT-ICR mass spectra show Al_9^- as the only major reaction product at *m/z* = 242.9 after up to 400 s of exposure to $^3O_2$ and $^1O_2/^3O_2$.

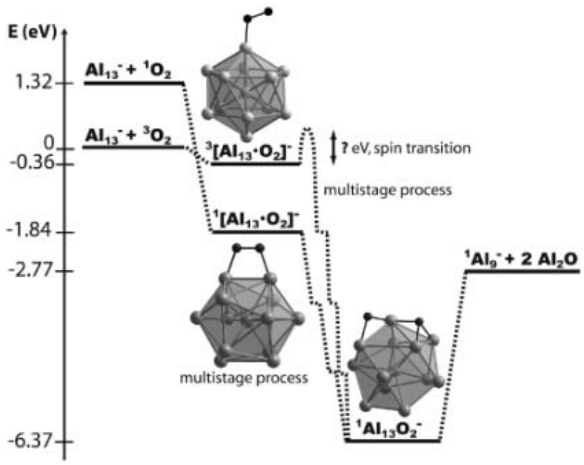

Fig. 3. Energy diagram (calculated) for the interaction of $^1O_2$ and $^3O_2$ on the Al_{13}^- cluster surface. The transition from $^3[Al_{13}{\cdot}O_2]^-$ to $^1Al_{13}O_2^-$ is estimated to be a multistage process in which O_2 is first bound side-on, then rearranges to end-on, after which the O-O bond is disrupted, new Al-O-bonds are formed (μ^3), and the spin state changes from triplet to singlet. In addition, the further degradation to Al_9^- and two Al_2O is displayed.

$$^1Al_{14}H^-(g) + {}^3O_2 \rightarrow {}^3[HAl_{14}{\cdot}O_2]^- \quad -1.43\ \text{eV} \quad (4a)$$

$$^1Al_{14}H^-(g) + {}^3O_2 \rightarrow {}^1Al_{10}H^-(g) + 2\ Al_2O(g) \quad (\mathbf{4})$$

$$^1Al_{13}^- + {}^1O_2 \rightarrow {}^1[Al_{13}{\cdot}O_2]^- \quad -3.16\ \text{eV} \quad (5a)$$

$$^1[Al_{13}{\cdot}O_2]^- \rightarrow {}^1Al_{13}O_2^- \quad -4.53\ \text{eV} \quad (5b)$$

$$^1Al_{13}O_2^- \rightarrow {}^1Al_9^- + 2\ Al_2O \quad 3.60\ \text{eV} \quad (5c)$$

$$^1Al_{13}^- + {}^1O_2 \rightarrow {}^1Al_9^- + 2\ Al_2O \quad -4.09\ \text{eV} \quad (\mathbf{5})$$

In the reaction of Al_{13}^- with $^1O_2$, $^1[Al_{13}{\cdot}O_2]^-$ is expected to form in its singlet state (Eq. 5a). In the course of further reaction through $^1Al_{13}O_2^-$ (in which O_2 is dissociated) to the products $^1Al_9^-$ and 2 Al_2O, all reaction steps are spin allowed (Eqs. 5b and 5c). In contrast to reactions with $^3O_2$, no spin transition is needed in the case of $^1O_2$, and therefore the reaction can proceed unimpeded.

Although $^1O_2$ is extremely short-lived in dense gases at pressures around 1 atm, the average lifetime of $^1O_2$ ($^1\Delta_g$) can be extended up to 3×10^3 s under collision-free conditions (pressure of ~10^{-8} mbar) (*22*), and experiments can be performed on this time scale. To generate $^1O_2$, we exposed $^3O_2$ to a static electrical discharge (Tesla coil) (*23*), yielding a $^1O_2/^3O_2$ mixture. Only $^1O_2$ molecules reacted at an appreciable rate with Al_{13}^-, and Al_9^- would be expected as the only product. As shown in Fig. 2, Al_{13}^- was degraded to Al_9^- in a $^1O_2$-containing atmosphere. The large excess of $^3O_2$ did not affect the experiment to an appreciable extent because the reaction of Al_{13}^- with $^3O_2$ is much slower [Fig. 2 (left)].

Tesla coil discharges can also induce formation of O atoms. If O atoms were to survive without reacting with the apparatus walls, they could potentially react with Al_{13}^- to form Al_{11}^- as indicated in Eq. 6. However, as shown in Fig. 2 (right), no Al_{11}^- formation was observed.

$$Al_{13}^-(g) + O \rightarrow Al_{11}^-(g) + Al_2O(g) \quad (\mathbf{6})$$

$$^1Al_{13}^- + {}^1O_3 \rightarrow {}^1Al_{11}^- + Al_2O + {}^1O_2 \quad (\mathbf{7})$$

$$^1Al_{11}^- + {}^1O_3 \rightarrow {}^1Al_9^- + Al_2O + {}^1O_2 \quad (\mathbf{8})$$

In addition, ozone (O_3) could be formed in the discharge as well (*23*). To characterize the reactivity of O_3, we exposed Al_{13}^- clusters to a pure O_3 atmosphere (*23*). This experiment showed that Al_{13}^- decomposed into Al_{11}^- and Al_9^-, as well as into Al_2O as coproduct (fig. S2 and Eqs. 7 and 8). Ozone has a singlet electronic ground state, and therefore all reaction steps are spin-allowed. As shown in Fig. 2 (right), Al_{11}^- is absent, indicating that O_3 was also not a major factor in the reaction of Al_{13}^- with the $^1O_2/^3O_2$ mixture. (*24*)

To support our experimental findings, we performed quantum chemical calculations at the second-order Møller-Plesset (MP2) level of theory with a triple-zeta polarization (TZVP) basis set using the Gaussian03 code (*25*). Coupled cluster with single, double and perturbative

triple excitations [CCSD(T)] single-point calculations were performed with the same basis set on MP2-optimized geometries. Unless otherwise noted, all energetic results reported here correspond to those obtained at the CCSD(T) level (*26*).

In modeling the odd/even effect, we assumed that the total reaction, wherein an Al_n^- cluster is reduced to two smaller fragments by oxygen, is a multistage process. In the initial step, O_2 interacts with the cluster to form an adduct, which further dissociates into the products Al_{n-4}^- and two Al_2O. The reactivity of a given cluster is determined by the nature of the initial interaction of O_2 with the cluster to form the adduct. Theoretical investigations on similar reactions between $^1O_2$ and unsaturated hydrocarbons (2 + 2 and 2 + 4 cycloadditions, "ene"-reactions) have revealed a puzzling array of reactive outcomes (*27*, *28*). Our calculations reveal that the initial interaction of O_2 with the cluster leads to an association complex, in which the O-O bond is slightly elongated, but remains intact (*29*). Subsequently, there is a strong bond formation between Al atoms and O_2, which is the rate-determining step. By comparison, the reaction of $^3O_2$ with C=C systems proceeds similarly, first through formation of a C-C-O-O adduct and then dissociation to products (*28*). Next, we calculated the reaction energies for each cluster. The spin-allowed interaction of $^1O_2$ with Al_{13}^- leading to formation of $^1[Al_{13}{\cdot}O_2]^-$ is calculated to be highly exothermic by −3.16 eV (Eq. 5a). Reactions of $^1O_2$ with carbon-carbon bonds are known to be concerted. Therefore, we assume that both O-Al bonds are formed simultaneously (Fig. 3). In subsequent reaction steps, both O atoms separate to give $^1Al_{13}O_2^-$ (Eq. 5b). This multistage process in which O_2 dissociates and covalent Al-O bonds are formed is also calculated to be highly exothermic (−4.53 eV). As experimentally observed, Al_9^- and 2 Al_2O molecules are formed as final products of this reaction cascade. The degradation of $^1Al_{13}O_2^-$ to these products is calculated to be endothermic by 3.60 eV (Eq. 5c). Thus, the net reaction is exothermic by −4.09 eV.

Concerning the association reaction of Al_{13}^- with $^3O_2$, we found that the initial interaction is only slightly exothermic by −0.36 eV (−35 kJ mol^{-1}) (Eq. 1a). In contrast to reactions of $^1O_2$, the $^3O_2$ diradical reacts through a consecutive pathway with only one O-Al bond being formed in the first step (Fig. 3). We calculated the formation of $^2Al_{14}O_2^-$ to be exothermic by −2.76 eV (−267 kJ mol^{-1}) (Eq. 2a).

For reactions of aluminum hydride clusters with $^3O_2$, we observed a similar trend, where the formation of $^3[HAl_{14}{\cdot}O_2]^-$ (triplet state) is less exothermic than the formation of $^2[HAl_{13}{\cdot}O_2]^-$ (doublet state) (Eqs. 3a and 4a).

The calculations indicate that on an aluminum hydride cluster surface, the initial interaction of oxygen is again less exothermic if the intermediate adduct is formed in a triplet state.

As demonstrated by the calculations (Fig. 3), the formation of $^1Al_{13}O_2^-$ is highly exothermic, but its total heat of formation (−7.69 eV) cannot be dissipated under UHV conditions; as a result, $^1Al_{13}O_2^-$ fragments by loss of two Al_2O molecules within a few nanoseconds (SOM Text, section 2). The cleavage of Al_2O is endothermic and will absorb much of that energy (3.60 eV). Though the above reactions are all spin-allowed, it is noteworthy that the highly exothermic formation of $^1[Al_{13}{\cdot}O_2]^-$ (singlet state) from Al_{13}^- and $^3O_2$ is not probable according to spin conservation rules (Eq. 1d).

The results of the calculations indicate that the formation of the initial oxygen adducts of all theoretically considered systems are exothermic and therefore spontaneous. Yet, observing that the exothermicity trend ($Al_{14}^- > Al_{13}H^- > Al_{14}H^- > Al_{13}^-$) closely parallels the trend of their reactivity toward oxygen ($Al_{14}^- \sim Al_{13}H^- > Al_{14}H^- \gg Al_{13}^-$) led us to believe that although the spin-conservation factors must play a dominant role, to fully understand the kinetics of oxidation of these systems one has also to consider the energy factors. For example, systems forming a triplet initial adduct (e.g., Al_{13}^- and $Al_{14}H^-$) need to cross from their PES onto the PES of the singlet state (spin flip). As mentioned earlier, these transitions are inherently slow in light atom–containing species owing to their small spin-orbit coupling. In addition, crossing points between PESs of different spin states regularly occur at geometries different from that of the ground state, and therefore an energy barrier inherently accompanies these transitions. Consequently, a sufficient amount of energy is a necessary, yet not a sufficient condition, for spin flip reactions to proceed. For example, particularly stable systems such as the "double magic" Al_{13}^- do not release the required amount of energy upon adduct formation (−0.36 eV) to even reach the crossing point where the spin flip could occur. In contrast, the less-stable singlet systems such as $Al_{14}H^-$ and probably most other Al_{odd}^- and $Al_{even}H^-$ systems that release a considerable amount of energy upon adduct formation (e.g., −1.43 eV in the case of $Al_{14}H^-$) can likely reach the barrier energetically; however, these systems still suffer from the low probability of the transition between the two spin surfaces. This twofold control of kinetics could explain why among unreactive Al_{odd}^- and $Al_{even}H^-$ clusters, some clusters, most notably Al_{13}^-, prove particularly unreactive.

Thus, although the calculations could not fully illuminate the reactive pathway, they were nevertheless instructive and essentially supported our hypothesis: Reactions slow down if in accordance with spin conservation rules, the initial O_2 adduct is formed in a triplet state. This is true for pure Al clusters, as well as for Al cluster hydrides. When Al_{13}^- or $Al_{14}H^-$ react with $^3O_2$, the intermediate adducts are formed in a triplet state. Because the final products of these reactions are all in singlet states, there must be a spin transition in the course of the reaction cascades. In the case of $Al_{14}H^-$, the formation of $^3[HAl_{14}{\cdot}O_2]^-$ is exothermic by −1.43 eV. This step provides sufficient energy to eventually undergo a spin transition. Therefore, it is not surprising that reactions of $Al_{14}H^-$ and $^3O_2$ are slow in comparison with Al_{14}^-, but are much faster than reactions of Al_{13}^-, for which formation of $^3[Al_{13}{\cdot}O_2]^-$ is less exothermic (−0.36 eV).

In conclusion, we have shown that the reactivity of Al_n^- clusters with $^3O_2$ exhibits an odd/even trend that gets inverted upon addition of a single hydrogen atom. We furthermore demonstrated that Al_{13}^-, which reacts negligibly with $^3O_2$, reacts much more rapidly when exposed to even a small amount of $^1O_2$. These findings together represent direct experimental proof of the importance of spin in explaining the odd/even pattern observed for reactivities of Al clusters toward oxygen. It remains to be seen whether other systems can be experimentally shown to undergo similar selectivity. However, we speculate that as long as the reactant molecule exhibits a triplet state and the cluster series alternates in spin states, the spin restrictions may become crucial and cause clusters to exhibit the odd/even effect. In support of this idea, our recent study of similarly exothermic reactions of mass-selected Al_n^- clusters with Cl_2 showed only small differences in reactivities of neighboring Al clusters, agreeing with our expectations for a reactant in a singlet state ($^1Cl_2$) (*13*).

One implication of our study may have relevant consequences for catalysis. For example, deposited nanoparticles, clusters, or surface sites that possess specific spin states may exhibit highly selective catalytic behavior, arising from the difficulty of metal clusters containing light elements like aluminum to undergo a spin flip during the primary steps of a reaction (*20*). For clusters of heavier metal atoms with considerable spin-orbit coupling, this kind of selectivity may not be possible. Another important result is revealed when comparing the "double magic" Al_{13}^- super atom with the bulk metal (SOM Text, section 1). In both cases, there are marked topological (e.g., coordination number of the central atom is 12) and thermodynamic similarities (*13*, *14*) [e.g., the formation of solid Al_2O_3 from Al_{metal} and Al_{13}^- exhibits nearly the same reaction enthalpy $\Delta_R H^\circ$ (0 K): Eq. 9 (−3399 kJ mol^{-1}) and Eq. 10 (−3351 kJ mol^{-1})]. Within the error margin (theory and experiment), these enthalpy values equal the energy differences presented in Eqs. 1 to 5, 9, and 10. (Eqs. 9 and 10):

$$Al_{13}^-(g) + 3\ O_2 \rightarrow Al_9^-(g) + 2\ Al_2O_3(s) \quad -35.2\ eV \qquad (9)$$

$$4\ Al(bulk) + 3\ O_2 \rightarrow 2\ Al_2O_3(s) \quad -34.7\ eV \qquad (10)$$

Thus, Al_{13}^- may provide a suitable model for some aspects of the surface of bulk Al. If so, there may be an analogy between the slow reaction of

$^3O_2$ with bulk Al (*30*) and with the Al_{13}^- cluster. Because the interpretation of the low bulk reactivity remains unsettled, the results presented here may prove useful in unraveling the controversy surrounding the interpretation of solid-state aluminum reactivity. Furthermore, spin states play an important role in long-known oxidation processes (e.g., O_2/NO/NO_2; O_2/SO_2/SO_3), and also in the oxidation of carbon compounds: The first detailed experimental and theoretical data for $^1O_2$ reactions with 2 + 4 and 2 + 2 cycloadditions were presented only a decade ago (*28*). Thus, the present results may initiate further FT-ICR investigations of $^1O_2$ and $^3O_2$ reactions in many other chemical oxidation processes that affect our daily lives, e.g., in biology (respiration), engineering (corrosion), and energetics (combustion).

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Supporting Online Material

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SOM Text
Figs. S1 to S3
Table S1
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NMR Imaging of Catalytic Hydrogenation in Microreactors with the Use of para-Hydrogen

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Catalysis is vital to industrial chemistry, and the optimization of catalytic reactors attracts considerable resources. It has proven challenging to correlate the active regions in heterogeneous catalyst beds with morphology and to monitor multistep reactions within the bed. We demonstrate techniques, using magnetic resonance imaging and para-hydrogen (p-H_2) polarization, that allow direct visualization of gas-phase flow and the density of active catalyst in a packed-bed microreactor, as well as control over the dynamics of the polarized state in space and time to facilitate the study of subsequent reactions. These procedures are suitable for characterizing reactors and reactions in microfluidic devices where low sensitivity of conventional magnetic resonance would otherwise be the limiting factor.

Catalysis is a fundamental component to many industrial processes and, consequently, the optimization of catalytic reactions and reactors attracts considerable technological effort and financial commitments. An important aspect of this optimization is to correlate the spatial distribution of the reactive conversion inside the reactor with the morphology and packing of the catalyst. Here, we describe a spectroscopic method for this purpose based on magnetic resonance imaging (MRI) (*1*) that uses hyperpolarized spins derived from p-H_2 (*2*, *3*). Specifically, we achieve high-resolution, spatially resolved profiles of heterogeneous hydrogenation reactions taking place at a solid-gas interface inside a microreactor. We demonstrate strongly enhanced nuclear magnetic resonance (NMR) signal intensities in the gas phase as well as precise control over the spatiotemporal dynamics of the polarization. The enhanced sensitivity is particularly important for tracking gases and products in small volumes [e.g., in microfluidic devices (*4*, *5*) or the limited void space of a tightly packed catalyst bed]. Moreover, the controlled delivery of p-H_2–induced nuclear spin polarization acts as a spin label that can transport polarization to remote regions in the reactor. This work has implications for studying kinetics and mechanisms of multistep heterogeneously catalyzed reactions and fluid-flow transport, as well as mass and heat transfer. Such characterization should facilitate improved reactor and catalyst design.

Methods to optimize microreactors would be welcome in the context of microfluidic (lab-on-a-chip) technology. In recent years, the compelling advantages of microfluidic technology (*4*, *5*) in biopharmaceutical applications, chemical analysis (*6*), organic synthesis (*7*, *8*), and industrial catalysis have been recognized and demonstrated

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(*9*, *10*). These include smaller volumes and substantial economic savings, precise control of reactant delivery, improved fluid transport and heat dispersion, control of reaction rates, enhanced safety of highly exothermic or explosive processes, and the possibility of faster reactions, improved yield, and chemoselectivity. Recent developments in microfluidic technology also provide powerful means for performing complex reactions, such as multistep transformations (*9*) or multiphase reactions (*10*). Furthermore, the use of catalysts immobilized on solid supports in flow-mode microreactors has recently been shown to result in highly efficient reactions (*10*, *11*).

One important characterization for the optimization of catalyst bed reactors is the flow map. Knowledge of the velocity distribution of the reaction product enables study of transport phenomena within a microreactor (*12*–*14*) and optimization of the catalyst packing and reactor geometry. High flow uniformity in a catalytic converter is crucial for avoiding non-uniform deactivation of the catalyst caused by both chemical and thermal aging. With the increasing sophistication of mathematical modeling, such systems are routinely characterized by computational fluid dynamics. However, the relevance of such models is in doubt until they are validated against real measurements (*15*). This is particularly difficult in packed-bed microreactors where the methods available are limited to tracers and bulk (average) properties of temperature, conversion, and velocity. Despite the need for validation, the spatiotemporal distribution of reactants and products in heterogeneous systems has been seldom visited by chemical engineering researchers in recent years, owing to the substantial difficulties with performing quantitative measurements in situ (*15*).

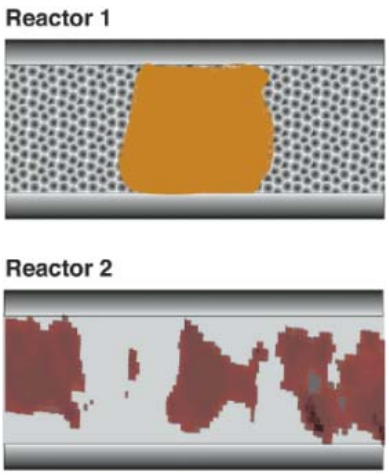

Fig. 1. Schematic of the microreactors. The two model catalytic reactors consist of catalyst layers sandwiched between layers of glass beads for stability. Reactor 1 contains a thin layer of silica gel–supported Wilkinson's catalyst (orange). Reactor 2 contains powdered Wilkinson's catalyst (red) arrayed in variously sized clumps to demonstrate a more heterogeneous scenario.

Various techniques have been used to study the motion of fluids in catalytic processes. For example, capacitance (*16*), single-photon emission–computed tomography (*17*), and positron emission tomography (*18*) are used to monitor gas-liquid distributions in multiphase reactors. But these methods measure average flow properties and have limited spatial resolution. The use of MRI to characterize microreactors is advantageous because the technique is noninvasive, can probe optically opaque media, and is appealing for catalysis because of the variety of molecular parameters that can be mapped with considerable chemical and spatial selectivity (*19*). Specifically, flow maps and local density profiles can be generated, molecular mobility can be tracked, and chemical reaction mechanisms can be probed with spin-labeled nuclei (*20*). Previous applications of MRI to heterogeneous catalysis included studies of hydrogenation processes without p-H_2 (*21*, *22*), catalyst morphologies and synthesis

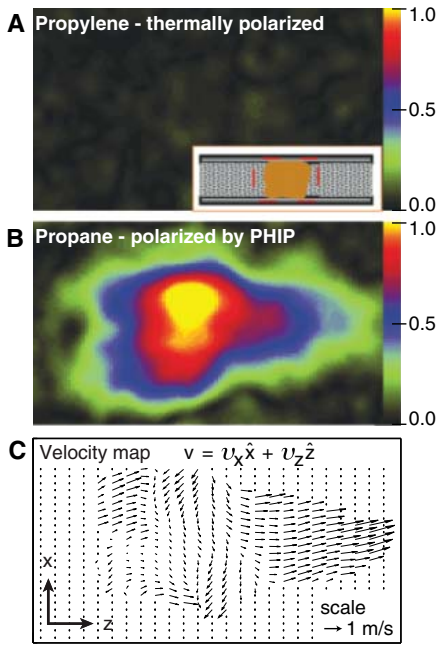

Fig. 2. Density of active catalyst and flow map imaging. MRI images [field of view (FOV) (*x* to *z*): 2.3 mm by 7.0 mm; pixel size: 20 μm by 60 μm] of a tightly packed catalyst bed (catalyst layer thickness is ~5 mm) are shown. (**A**) Thermally polarized propylene. The approximate position of the imaging FOV is indicated by the dashed red lines in the inset. (**B**) p-H_2–polarized propane. The signal-to-noise ratio (SNR) of this image is a factor of 300 larger than that of the thermally polarized propylene image. (**C**) Flow map in the *xz* plane with the use of polarized propane. The orientation of the arrows represents direction of the velocity, and their length represents its magnitude. The SNR of thermally polarized propylene was insufficient to generate a velocity map. The resolution of the flow map is intentionally decreased by retaining only 1 of every 16 arrows to avoid excessive overlap of the arrows.

techniques (*23*, *24*), and fluid flow through the catalyst bed (*25*), as well as monitoring of esterification reactions (*12*, *13*) in situ. All of these applications were based on the NMR signal detection of the liquid phase and thus offer a sensitivity that is three orders of magnitude larger as compared with gases, resulting from the difference in density. The sensitivity enhancement offered by p-H_2–induced polarization (PHIP) is essential for the application of MRI to heterogeneous chemical reactions in the gas phase.

p-H_2 (*2*, *3*, *26*) is characterized by a singlet nuclear spin wave function and is relatively easy to prepare in quantum-state ensembles of very high purity. The total nuclear spin angular momentum of this state is zero, resulting in no observable NMR signal. However, if the protons participate in pairwise hydrogenation in which they become magnetically inequivalent, strong observable magnetization can be produced (*2*, *3*, *26*) with a signal enhancement factor typically on the order of 10^4. For instance, if p-H_2 is used in the hydrogenation of propylene into propane (*27*, *28*), the p-H_2–derived protons will be in the singlet state immediately after the transformation of the substrate molecule into the product molecule. Typically, the molecular additions occur at randomly distributed times, and the result is an incoherent but highly polarized nuclear spin state. Application of suitable radio-frequency (rf) pulses results in a hyperpolarized NMR signal (*29*). However, if an isotropic mixing sequence is applied during the course of the reaction, not only is a coherent singlet state preserved, but the lifetime of this state is also increased (*30*). As we demonstrate below, this effect allows one to create a relatively long-lived, coherent packet of polarized product molecules, which augments the versatility of this technique beyond hydrogenation reactions.

To demonstrate the effectiveness of heterogeneously catalyzed PHIP in microreactors, we use two model catalytic reactors (*29*) (Fig. 1). In both cases, propylene and p-H_2 gases are flowed through the catalyst bed and react to form propane. The first reactor (reactor 1) contains a tightly packed bed of the silica gel–immobilized Wilkinson's catalyst located between two layers of glass beads. This reactor is used to produce a highly polarized product (propane) and illustrates the ability to resolve flow maps, active regions in the catalyst bed, and controlled transport of polarization out of the catalyst bed. The second reactor (reactor 2) comprises powdered Wilkinson's catalyst loosely packed with some small (~2-mm) air gaps. This second reactor further demonstrates the control of a polarized outstream and applications to a more heterogeneous packing.

The PHIP signal in these experiments is larger than the corresponding thermal signal by a factor of 300 (*29*). This enhancement is crucial in light of the coil-sample arrangement. The ratio of the rf coil volume occupied by the microchannel to the rf coil volume is less than 0.01: a situation that is unfavorable in terms of detection

sensitivity. Furthermore, the presence of catalyst powder occludes the space inside the microchannel. This sensitivity loss, combined with the low density of the gas, leads to a million-fold loss in sensitivity relative to standard liquid-state NMR. Our experimental results show that PHIP can, to a large extent, circumvent the problem of low sensitivities in gas-phase microreactors.

An image of the first reactor is shown in Fig. 2. The spatial distribution of reactant (propylene) is barely resolved (Fig. 2A), whereas the polarized product (propane) shows a strongly enhanced signal (Fig. 2B). We also compare a spectrum from the reactor (fig. S2A) and localized spectra from upstream of (fig. S2B) and in (fig. S2C) the catalyst bed. The use of a hyperpolarized substance was also necessary for producing the high-resolution gas-phase flow map shown in Fig. 2C (*29*). This example reveals heterogeneous flow patterns in the catalyst bed, which are consistent with a non-uniform packing of the catalyst (*29*), that are not apparent in Fig. 2B. Flow imaging at the same resolution and sensitivity would not be possible with the exceedingly weak thermal signals.

As illustrated in Fig. 3A, the residence time inside the tightly packed region leads to nearly complete magnetic relaxation, and no polarized product is observed beyond the catalyst bed. Although this outcome is ideal for imaging the active regions of the catalyst bed, the polarized spins cannot be used for subsequent reactions. Isotropic mixing sequences have been shown to prolong the lifetime of the nuclear spin-singlet state (*30*). Thus, the use of an isotropic mixing sequence (*31*) applied for a sufficiently long duration T_m allows the polarized product to escape the catalyst bed (the optimal T_m will depend on the average flow velocity v). This period is followed by a delay T_d, allowing the singlet state to travel a distance $x = v \times T_d$, during which the singlet state evolves into a state observable by NMR. By varying T_d, we control the distance traveled before the polarization is released. Figure 3, B and C, demonstrates the delivery of polarized product beyond the catalyst bed for two values of T_d.

Imaging of the second reactor (Fig. 4A) further demonstrates the usefulness of controlling the polarized outstream. In contrast with the packing in reactor 1, the looser packing in reactor 2 results in a polarized product that can be seen escaping the first catalyst layer and flowing to the second layer in the absence of singlet state preservation (T_m = 0 ms, T_d = 0 ms). Although this situation is desirable when the polarized product is to be used in subsequent reactions, it is problematic as a means for imaging the catalyst layer because of poor contrast and blurring from the uncontrolled flow of polarized product. This drawback can be remedied by controlling the singlet state as follows. For short values of T_d (1 ms), no polarized product can be seen between the catalyst layers, because the singlet state has not yet evolved into an observable state. At longer time intervals (T_d = 100 ms), the polarized product has traversed longer distances and evolved into an observable polarized product. A photograph of the reactor (Fig. 4B) provides a comparison of the distribution of catalyst in the reactor with the structural morphology observed in the MRI images.

Regardless of the packing, singlet state preservation provides a distinctive method for controlled delivery of polarization. Combined with knowledge of the local flow velocity, the timed release of polarization can be performed in remote parts of a microreactor. Thus, in multistep reactions, the polarized product can be used as a spin label to elucidate subsequent stages of a reaction (*20*).

These experiments can be extended by means of a variety of polarization transfer and spin manipulation methods to move the enhanced signal to other NMR-active nuclei on the substrate molecule or onto the catalyst itself (*14*, *20*). Transfer of polarization to heteronuclei yields a larger range of chemical shifts as compared with that of protons (*14*). The highly polarized spin product also makes it possible to image flows (*32*) and reactions (*33*) in precisely engineered microchannels noninvasively, opening the way for a variety of microfluidic applications.

There are still many challenges to address before these results can be extended to a wider range of hydrogenation reactions and conditions of industrial catalytic processes. In particular, it remains to be seen to what extent the polarization lifetimes and the NMR linewidths of the reaction products are affected by the presence of metal catalyst surfaces, microscopic gradients of magnetic susceptibility, high temperatures, paramagnetic catalysts and impurities, liquid films, and other complications that can be expected under conditions encountered in practice. To this end, recent results (*34*) that demonstrate PHIP in heterogeneous hydrogenations catalyzed by supported metal catalysts (Pt/Al_2O_3 and Pd/Al_2O_3) are encouraging.

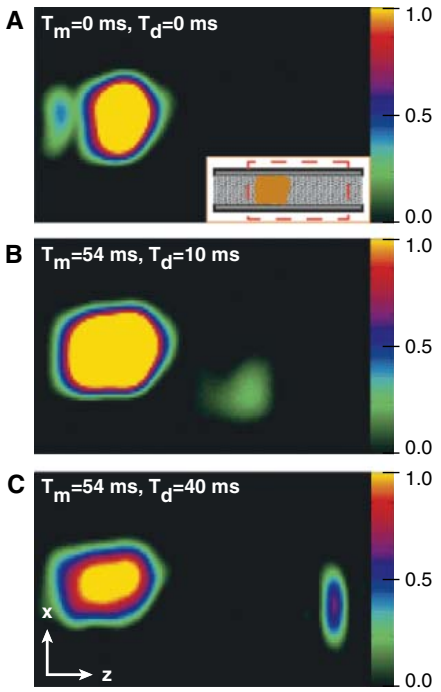

Fig. 3. Controlled transport of polarized product. MRI images [FOV (*x* to *z*): 8.5 mm by 23 mm; pixel size: 0.5 mm by 1 mm] for different travel times after an isotropic mixing sequence are shown. (**A**) No isotropic mixing: The polarized product is observed only in the catalyst layer. The approximate position of the imaging FOV is indicated by the dashed red lines in the inset. (**B**) Ten milliseconds after isotropic mixing, the polarized product travels 5 mm. (**C**) Forty milliseconds after isotropic mixing, the product has traveled 10 mm.

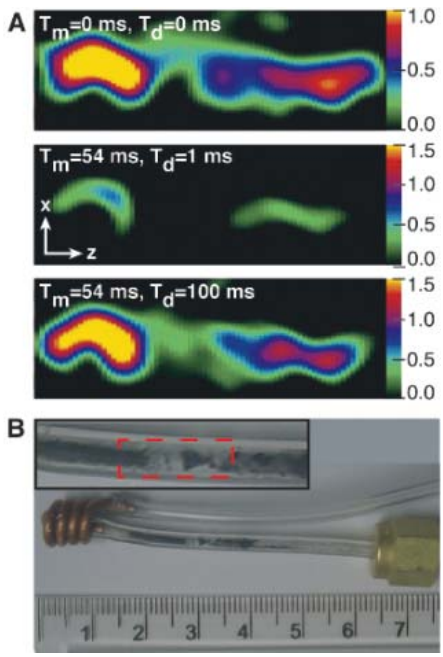

Fig. 4. Imaging heterogeneous distributions of catalyst. (**A**) MRI images [FOV (*x* to *z*): 2 mm by 15 mm; pixel size: 0.4 mm by 0.9 mm] of the heterogeneous packing, acquired without isotropic mixing (T_m = 0 ms, T_d = 0 ms) and for two different travel time intervals (T_d = 1 and 100 ms) after 54 ms of isotropic mixing. (**B**) Catalytic reactor containing a heterogeneous packing of Wilkinson's catalyst powder mixed with glass beads. An enlarged view of the catalyst packing is shown in the inset. The dashed red lines indicate the approximate location of the FOV for the images in (A).

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Supporting Online Material

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Materials and Methods
Figs. S1 and S2
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GaN Photonic-Crystal Surface-Emitting Laser at Blue-Violet Wavelengths

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Shorter-wavelength surface-emitting laser sources are important for a variety of fields, including photonics, information processing, and biology. We report on the creation of a current-driven blue-violet photonic-crystal surface-emitting laser. We have developed a fabrication method, named "air holes retained over growth," in order to construct a two-dimensional gallium nitride (GaN)/air photonic-crystal structure. The resulting periodic structure has a photonic-crystal band-edge effect sufficient for the successful operation of a current-injection surface-emitting laser. This represents an important step in the development of laser sources that could be focused to a size much less than the wavelength and be integrated two-dimensionally at such short wavelengths.

The lasing principle of photonic-crystal surface-emitting lasers (PC-SELs) (*1*–*5*) is based on the band-edge effect in a two-dimensional (2D) PC, where the group velocity of light becomes zero and a 2D cavity mode is formed. The output power is coupled to the vertical direction by the PC itself, which gives rise to the surface-emitting function. PC-SELs have the following features: first, perfect, single longitudinal and lateral mode oscillation can be achieved even when the lasing area becomes very large (for example, devices >300 μm in diameter) (*1*, *3*, *5*); second, the polarization mode (*3*) and the beam pattern (*5*) can be controlled by appropriate design of the unit cell and/or lattice phase in the 2D PC. However, the shortest lasing wavelength achieved so far is 980 nm. A lasing wavelength in the blue-to-ultraviolet region would open the door to a much broader range of applications such as super–high-resolution laser sources, which can be focused to spot sizes smaller than blue-violet wavelengths by the use of doughnut beams (*5*, *6*), and optical tweezers for ultrafine manipulation.

One issue in the creation of a gallium nitride (GaN)–based PC-SEL has been whether a 2D PC structure could be constructed with a sufficient band-edge effect. To do so requires the fabrication of a high-quality 2D GaN/air periodic struc-

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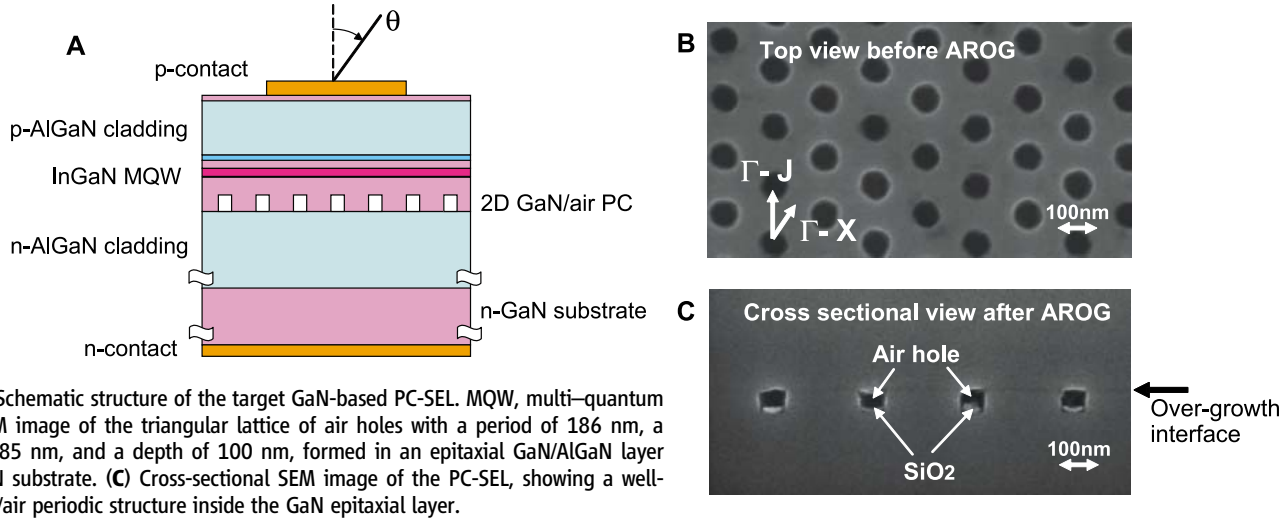

Fig. 1. (**A**) Schematic structure of the target GaN-based PC-SEL. MQW, multi–quantum well. (**B**) SEM image of the triangular lattice of air holes with a period of 186 nm, a diameter of 85 nm, and a depth of 100 nm, formed in an epitaxial GaN/AlGaN layer above a GaN substrate. (**C**) Cross-sectional SEM image of the PC-SEL, showing a well-defined GaN/air periodic structure inside the GaN epitaxial layer.

ture with a lattice constant between 100 and 200 nm, close to an active layer with optical gain. Figure 1A shows the schematic structure of the target GaN-based PC-SEL. In order to obtain the required band-edge effect, the PC structure must be constructed within 300 nm of the active layer.

Previously, 2D semiconductor/air PC structures in PC-SELs have generally been constructed using a wafer-fusion technique (*1*, *3*, *5*), in which one of the important processes is to remove the sacrificial substrate after the 2D semiconductor/air periodic structure has been formed. Although there are several reports on sacrificial etching techniques in GaN systems (*7*, *8*), the application of these processes for the fabrication of PC-SELs has not yet been established. We therefore developed a new method, "air holes retained over growth" (AROG), for the construction of such a periodic structure. Our method is based on the particular characteristics of GaN growth; namely, that growth proceeds much faster in the lateral direction than it does vertically from the (0001) crystal plane (*9*). Initially, a triangular lattice of air holes (Fig. 1B) with a period of 186 nm, a diameter of 85 nm, and a depth of 100 nm was formed in an epitaxial GaN/aluminum gallium nitride (AlGaN) layer situated above a GaN substrate, and a silicon dioxide (SiO_2) layer was then deposited at the bottom of each air hole. The GaN layer was then overgrown by means of a low-pressure metal-organic vapor-phase epitaxial method. Further fabrication details are described in fig. S1 (*10*). Figure 1C shows a cross-sectional scanning electron microscope (SEM) image of our fabricated device. The periodic arrangement of air holes was well defined inside the GaN epitaxial layer. The GaN overgrowth appeared to proceed laterally, capping the top of the air holes, whereas the SiO_2 deposited at the bottom of the air holes had a growth-blocking action (*10*). The structures of the air holes were essentially uniform and had not been degraded by the overgrowth process. Transmission electron microscopy confirmed that no dislocations were generated at the overgrowth interface (fig. S2) (*10*). The establishment of this AROG method allowed the formation of a 2D GaN/air PC structure near the active layer in the GaN system.

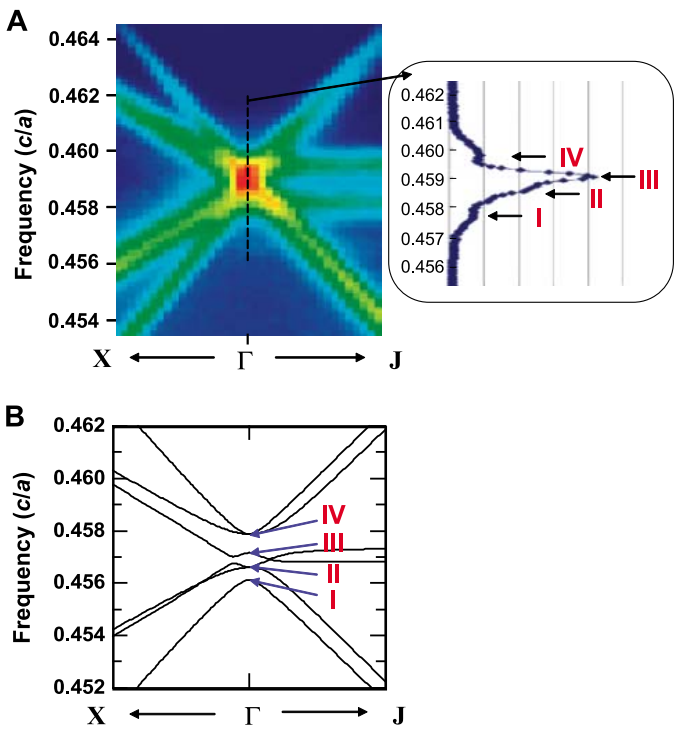

Fig. 2. (**A**) Measured 2D photonic band structure of the GaN/air periodic structure constructed with the AROG method. *c*/*a* , the unit of normalized frequency, where *c* is the velocity of light in vacuum and *a* is the lattice constant. The inset shows the spectrum observed at the Γ point, where four peaks (I, II, III, and IV) are resolved. (**B**) Band structure calculated by the plane wave-expansion method.

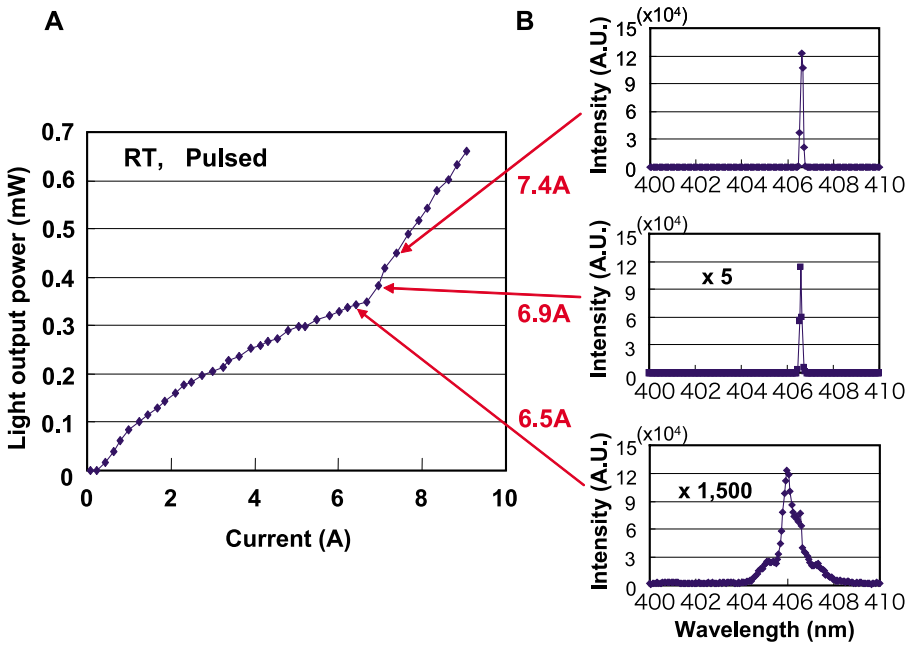

Fig. 3. (**A**) Current–light-output power characteristics of the device under the pulsed condition (a pulse width of 500 ns and a repetition rate of 1 kHz) at room temperature (RT). (**B**) Emission spectra above and below the current threshold. A.U., arbitrary units.

To investigate whether our periodic structure possessed the characteristics of a 2D PC, we measured the photonic band structure of our device by observing the resonant coupling of light from the active layer to the bands of the 2D GaN/air periodic structure (*11*). For a given frequency, resonant coupling occurs when the in-plane wave vector of the light matches the wave vector of the photonic bands. In spontaneous emission spectra, this coupling can be observed as a sharp peak. The in-plane wave vector k is related to the polar angle θ (shown in Fig. 1A) by the relation $k = (2\pi/\lambda_0)\sin\theta$, where λ_0 is the wavelength of the light in free space. By varying the θ defined with respect to the direction normal to the plane, and shifting the in-plane direction from Γ–X to Γ–J, which are the two characteristic directions of the 2D triangular lattice (shown in Fig. 1B), the photonic bands can be mapped out around the Γ point (fig. S3) (*10*). Figure 2A shows the results of the measurements, for which the injection current to the device was set at 20 mA. Figure 2B shows the band structure of the device, which was calculated by the plane wave-expansion method (*12*). The two figures seem to be in good agreement, especially for the central mode splitting (Γ point). As the in-plane k vector was increased, four peaks (denoted by I, II, III, and IV, respectively, in the inset of Fig. 2A) could be distinguished for the normal direction (Γ point); thus, four dispersion bands, including degenerate (or closely placed) bands, were constructed. These results indicate that the 2D GaN/air periodic structure formed in the device has the characteristics of a 2D PC. Moreover, based on 2D-coupled wave theory (*13*, *14*) for a triangular-

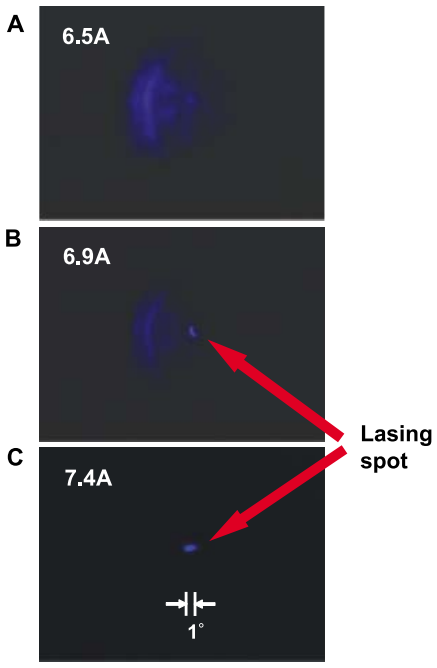

Fig. 4. (**A**) FFP observed below the threshold current (6.7 A) by setting a fluorescent substance at a distance of 10 cm above the device. (**B** and **C**) FFPs observed above the threshold (6.9 and 7.4 A, respectively).

lattice PC, the frequencies of the four peaks shown in the inset of Fig. 2A can be used to determine the 2D optical coupling coefficients κ_1, κ_2, and κ_3, which quantify the in-plane optical coupling effects for light waves propagating along the six equivalent Γ–X directions at 60°, 120°, and 180° to each other. Coefficients of $\kappa_1 \sim 830\ cm^{-1}$, $\kappa_2 \sim 510\ cm^{-1}$, and $\kappa_3 \sim 160\ cm^{-1}$, respectively, were obtained (*10*). Because the 2D band-edge effect is determined by the product of the coupling coefficients and the light-propagation length, we fixed the active PC area, where the current was injected, to $100 \times 100\ \mu m^2$ in order to obtain sufficient band-edge effects.

We then measured the current–light-output power characteristics (*10*) of our device under the pulsed condition (a pulse width of 500 ns and a repetition rate of 1 kHz) at room temperature (Fig. 3A). A clear threshold characteristic at 6.7 A (equivalent to a current density of 67 kA/cm^2) was apparent. Figure 3B shows the emission spectra below and above the threshold. The spectra were measured by coupling the output light from the device to an optical fiber and then transferring it to a monochromator (*10*). Below the threshold current (6.5 A), the emission spectrum was broad, and four peaks were observed with a distribution similar to that shown in the inset of Fig. 2A. In contrast, the spectrum became sharp with a peak width of ~0.15 nm above the threshold (6.9 and 7.4 A), which was close to the resolution limit of the measurement system. The peak wavelength was 406.5 nm (in the blue-violet region). The emission peak above the threshold was much stronger than that below the threshold, which is due to substantial improvement in the optical coupling between the output and the optical fiber (*10*). Finally, we measured the far-field pattern (FFP) below and above the threshold by placing a fluorescent substance at a distance of 10 cm above the device. Because of the need to insert a digital camera to record the FFP, it was not possible to align the fluorescent substance completely parallel to the device surface, which resulted in slightly asymmetric FFPs (Fig. 4). The FFP was broad below the threshold current (6.5 A) but was reduced to a small spot above the threshold (6.9 and 7.4 A). The beam divergence angle was as narrow as 1°, which indicated that large-area coherent lasing oscillation had been achieved, reflecting the characteristics of the PC-SEL.

At present, the laser operates with a large threshold current; however, the performance could be substantially improved by the following methods: (i) Improvement of the crystalline quality of the multiple–quantum-well active layer. Currently, the growth condition of the active layer on the 2D GaN/air PC formed by AROG process has not yet been optimized. Modification of growth conditions such as growth pressure and III-V ratio would improve the quality of the active layer. (ii) Optimization of the distance between the active layer and the PC. Currently, the distance is ~150 nm, and the degree of mode overlap with the air holes is limited to ~3.5% (fig. S1) (*10*). If this distance were reduced to, for example, ~60 nm, the band-edge effect could be increased, causing the threshold current to be substantially reduced. (iii) Use of a transparent electrode. Currently, the top electrode is not transparent and thus blocks much of the surface emission. If a transparent electrode (or ring-type electrode) were used, the output power and/or efficiency could be improved.

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Comparison of Comet 81P/Wild 2 Dust with Interplanetary Dust from Comets

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The Stardust mission returned the first sample of a known outer solar system body, comet 81P/Wild 2, to Earth. The sample was expected to resemble chondritic porous interplanetary dust particles because many, and possibly all, such particles are derived from comets. Here, we report that the most abundant and most recognizable silicate materials in chondritic porous interplanetary dust particles appear to be absent from the returned sample, indicating that indigenous outer nebula material is probably rare in 81P/Wild 2. Instead, the sample resembles chondritic meteorites from the asteroid belt, composed mostly of inner solar nebula materials. This surprising finding emphasizes the petrogenetic continuum between comets and asteroids and elevates the astrophysical importance of stratospheric chondritic porous interplanetary dust particles as a precious source of the most cosmically primitive astromaterials.

The Stardust spacecraft collected thousands of comet dust particles measuring micrometers in size during its 6.1-km/s flight through the dusty coma and jets of comet 81P/Wild 2 (*1*–*4*). The dust was captured in optically clear, low-density, silica (SiO_2) aerogel and aluminum foils. Comet 81P/Wild 2 is believed to originate in the Kuiper belt (*1*), a ring of icy objects extending from the orbit of Neptune at ~19 astronomical units (AU) out to ~50 AU (*5*). 81P/Wild 2 orbited between 5.0 and 19 AU with an ~40-year period until perturbed by Jupiter's gravity in 1974 (*6*). The modified orbit provided a rare favorable opportunity for a low-relative-

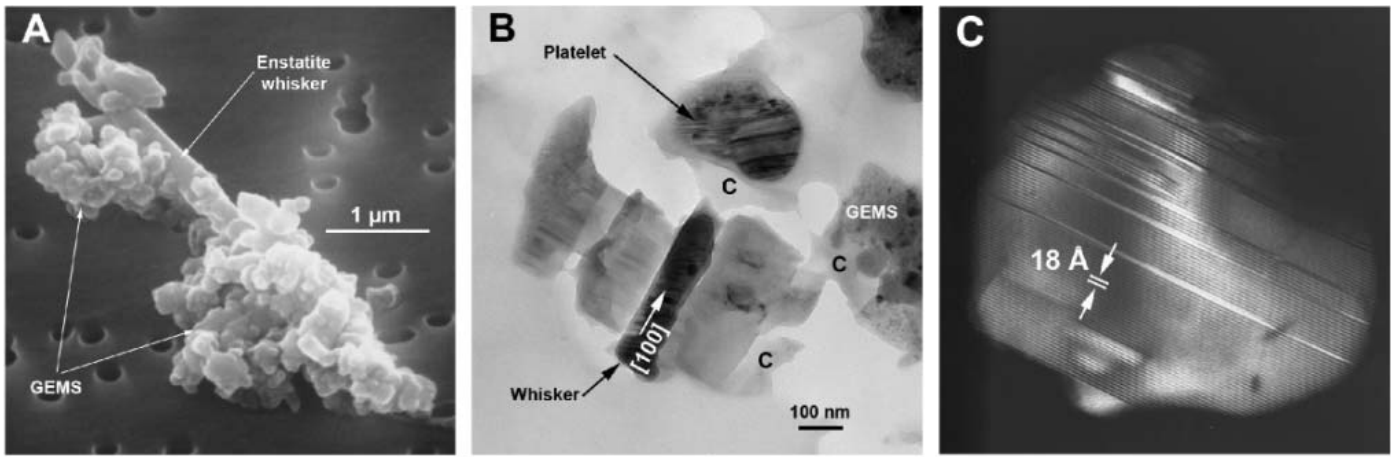

Fig. 1. CP IDP components. (**A**) Secondary electron image of CP IDP U25A30B mounted on a Nuclepore substrate. (**B**) Bright-field transmission electron micrograph of enstatite whiskers, platelets, GEMS, and carbonaceous material (C) in CP IDP U220A19. (**C**) Dark-field transmission electron micrograph of a <100-nm-thick enstatite platelet [systematics (h00) orientation] exhibiting 18 Å periodicity and numerous stacking defects in CP IDP CP16α.

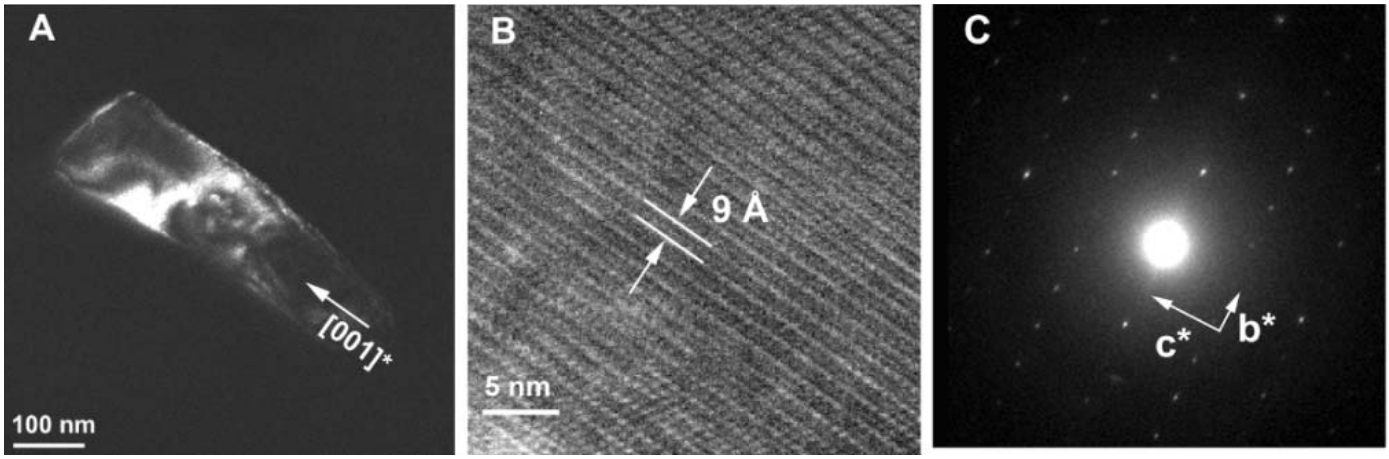

Fig. 2. Enstatite whisker in comet 81P/Wild 2 sample. (**A**) Dark-field transmission electron micrograph of a clino-enstatite whisker in Stardust track C2115,33,123,1,3 (Lucia). (**B**) Lattice-fringe image of the whisker showing 9 Å (010) lattice fringes. (**C**) [100] zone axis selected-area electron diffraction pattern.

velocity encounter. The comet experienced only five near-solar passes before the Stardust encounter, so solar processing of its surface was minimal, and 81P/Wild 2 has been widely anticipated to be a reservoir of presolar material, including stardust, cryogenically preserved since the accretion of the planets.

The returned sample was expected to include materials found in chondritic porous (CP) interplanetary dust particles (IDPs). Many IDPs entering Earth's atmosphere are from comets, and CP IDPs collected in the stratosphere by aircraft exhibit properties consistent with cometary origin (*7*–*9*). Some CP IDPs are demonstrably cosmically primitive: Relative to other extraterrestrial materials, they are highly enriched in isotopically anomalous organic and inorganic outer solar nebula materials inherited, via the presolar molecular cloud, from the interstellar medium and circumstellar environments around other stars (*10*, *11*). Although IDPs have been collected for ~40 years, the Stardust sample is a potential mother lode of presolar material from a known parent body containing 10^5 to 10^6 times the mass of an individual CP IDP and ~10^3 to 10^4 times the total mass of all CP IDPs examined to date.

Analysis of comet 81P/Wild 2 dust has revealed, in addition to silicates (olivines and pyroxenes) with a range of Mg to Fe ratios (*4*), refractory minerals formed in the inner nebula, probably within a few astronomical units of the early Sun. Minerals identified include melilite, anorthite, corundum, osbornite and roedderite associated as calcium-aluminum inclusions (CAIs), and probable chondrule fragments (*4*, *12*). Refractory minerals, CAIs, chondrules, and chondrule fragments are normally absent from or exceedingly rare in CP IDPs but are found in almost all chondritic meteorites. Stardust has thus provided solid evidence of large-scale radial mixing in the solar nebula (*1*, *4*), underscoring the importance of sample return missions.

CP IDPs contain two silicate materials believed to be unique to this class of meteoritic materials: amorphous silicates known as GEMS (glass with embedded metal and sulfides) that make up >50% by volume of most CP IDPs (*8*, *13*), and exotic whisker and platelet morphologies of the crystalline silicate enstatite. Enstatite whiskers and/or platelets are present in all CP IDPs (*14*), constituting 1 to 5% by volume. A secondary electron image of a CP IDP (Fig. 1A) shows typical porous morphology (mostly GEMS) and an elongated enstatite crystal (a whisker). The typical petrographic setting of GEMS, enstatite whiskers, and platelets within CP IDPs is shown in a transmission electron micrograph from another CP IDP (Fig. 1B).

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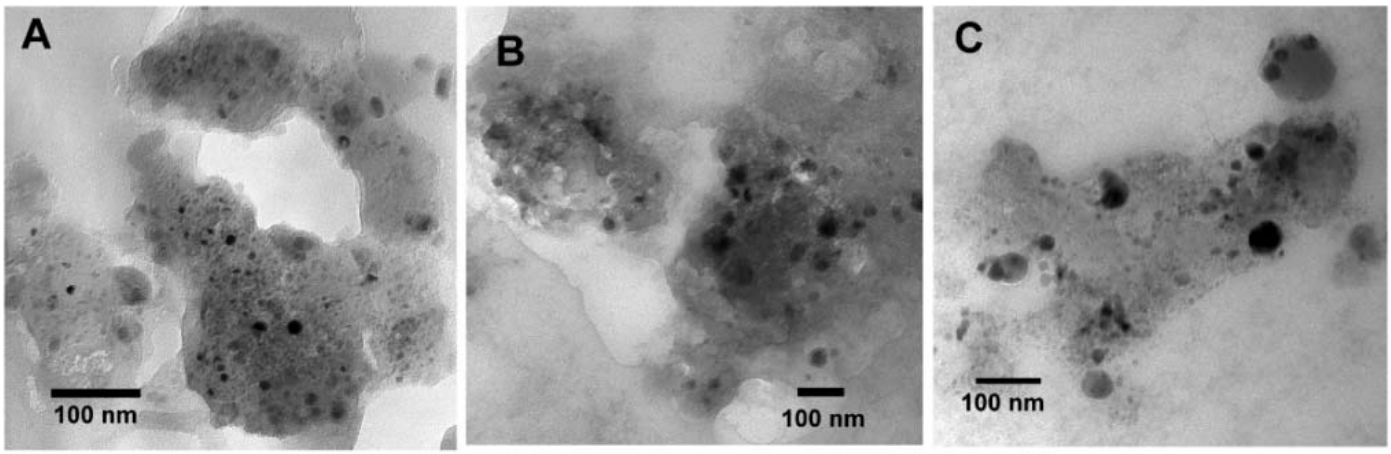

Fig. 3. GEMS and GEMS-like objects. Bright-field transmission electron micrographs of (**A**) GEMS in CP IDP U220A19, (**B**) GEMS-like material in Stardust track FC5,2,5,0,13 (Hopeful), and (**C**) GEMS-like material produced by a light gas gun–generated hypervelocity impact of a pyrrhotite grain into aerogel at Stardust impact velocity.

Table 1. Bulk compositions of GEMS-like objects and GEMS. The mean, median, standard deviation, minimum, and maximum values of bulk compositions in atomic percent are given below for GEMS-like objects in Stardust tracks and GEMS in CP IDPs.

	GEMS-like objects in Stardust (n = 46)					GEMS in CP IDPs (n = 42)				
Atomic %	Mean	Median	SD.	Min.	Max.	Mean	Median	SD.	Min.	Max.
O	66.41	67.28	4.47	52.41	72.68	62.71	63.22	4.43	49.29	75.30
Mg	2.05	1.28	1.83	0.00	7.41	9.37	9.95	4.42	1.20	16.21
Al	1.42	1.20	1.27	0.00	5.92	1.62	1.29	1.09	0.25	5.90
Si	24.44	25.05	4.24	13.71	30.74	14.40	14.17	2.36	9.96	19.10
S	1.13	0.59	2.34	0.00	13.49	3.69	2.72	2.73	0.64	12.97
Ca	1.47	0.23	2.54	0.00	10.87	0.82	0.81	0.70	0.00	3.53
Cr	0.00	0.00	0.00	0.00	0.00	0.12	0.12	0.10	0.00	0.43
Mn	0.00	0.00	0.03	0.00	0.17	0.02	0.00	0.06	0.00	0.28
Fe	2.79	1.51	3.02	0.24	12.19	6.39	6.60	2.39	1.96	11.10
Ni	0.12	0.00	0.26	0.00	1.44	0.40	0.39	0.23	0.00	1.00

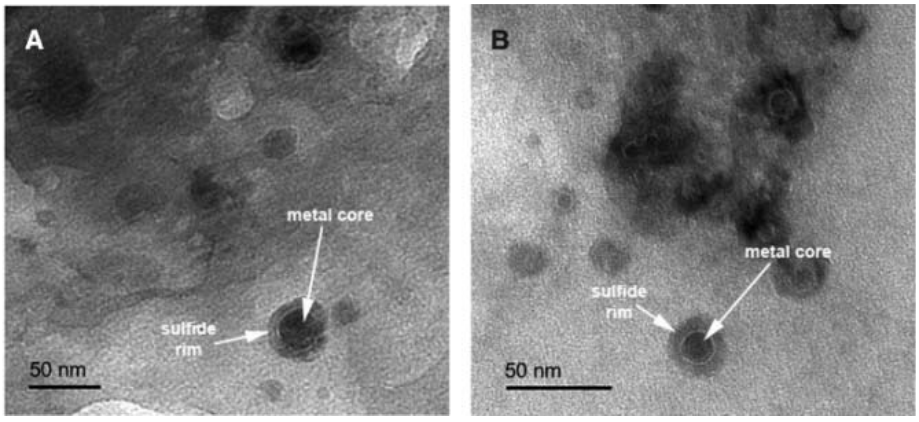

Fig. 4. Bright-field electron micrographs of sulfide grains after hypervelocity impact into aerogel at 6.1 km/s. (**A**) Stardust sample FC5,2,5,0,13 (Hopeful) shows sulfide rims on reduced metal cores. (**B**) Pyrrhotite laboratory shot fired at Stardust capture velocity into aerogel also results in sulfide rims on reduced metal cores.

Enstatite whiskers in CP IDPs are unique in that they are always elongated along the [100] crystallographic axis (*14*–*16*). In contrast, enstatite crystals in terrestrial rocks and meteorites, when not equiaxial, are elongated along [001]. Enstatite platelets in CP IDPs (*15*) include both ortho- and clino-enstatite and are extremely thin along the [010] or [001] direction but not [100] (Fig. 1C). These enstatite whiskers and platelets probably condensed metastably above 1300 K from a low-pressure nebular gas (*14*). If 81P/Wild 2 accreted substantial quantities of outer nebula primitive materials, then the Stardust sample should contain both GEMS and enstatite in whisker and platelet forms. Conversely, if 81P/Wild 2 contains mostly inner nebula materials as do the asteroid parent bodies of chondritic meteorites, then primitive material is rare in this comet, and from an astromaterials analysis standpoint, less-modified, larger quantities of Stardust-captured solids may be available in the existing meteorite collections. To explore these possibilities, we compared enstatite whiskers, GEMS, and GEMS-like materials in CP IDPs, Stardust samples, and laboratory samples using transmission electron microscopy (*9*).

A transmission electron micrograph (Fig. 2A) shows an elongated enstatite crystal in a Stardust impact track. Its morphology (Figs. 1B and 2A) and composition, almost pure $MgSiO_3$ with <0.5 weight % (wt %) Fe, are similar to those of enstatite whiskers in CP IDPs. Lattice-fringe imaging (Fig. 2B) and corresponding electron diffraction (Fig. 2C) establish that the crystal is monoclinic clino-enstatite. However, unlike whiskers in CP IDPs, this crystal is elongated along its [001]* axis. This is the only whiskerlike crystal we observed in the Stardust sample, although other enstatite crystals without whisker or platelet morphologies are present (*4*).

Typical GEMS in CP IDPs (Fig. 3A) are spheroids ~0.1 to 0.5 μm in diameter, composed of nanometer-sized inclusions of low-Ni α-iron (kamacite) and low-Ni iron sulfide (2C pyrrhotite) embedded in Mg-rich silicate glass (*8*, *13*, *17*). Some, and possibly all, GEMS are ancient (>4.6 billion years old) presolar interstellar amorphous silicates, a fundamental building material of solar systems (*8*, *9*, *13*, *18*). GEMS-like material (Fig. 3B), abundant in some Stardust tracks particularly those containing sulfide particles, was initially interpreted as a promising link between 81P/Wild 2 and CP IDPs (*3*, *4*). Like GEMS, it contains nanometer-sized inclusions of FeNi metal and sulfides embedded in glass. Unlike GEMS, the glass is

most often low-Mg silica (0 to 2 atomic % Mg), metal inclusions include both low-Ni α-iron and high-Ni γ-iron (taenite), sulfide inclusions often are partly reduced, and some sulfides contain Cu (*4*, *19*). Table 1 shows that bulk compositions of GEMS-like material in Stardust tracks differ substantially from GEMS in CP IDPs (*9*). On average, the former has higher Si (by a factor of nearly 2) and lower Mg and Fe relative to the latter. A laboratory light gas gun shot (*9*) of micrometer-sized pyrrhotite particles into aerogel at 6 km/s resulted in abundant GEMS-like material (Fig. 3C) in each impact track above a remnant pyrrhotite particle. This material consists of nanometer-sized inclusions of metal and sulfides embedded in Mg-free silicate glass (compressed and melted aerogel). Like the Stardust GEMS-like material (Fig. 4A), many sulfide inclusions in this material produced by a laboratory-generated impact have reduced metal cores (Fig. 4B). This distinctive association demonstrates unequivocally that in Stardust tracks, GEMS-like material was created during capture by melting and intermixing of aerogel with crystalline minerals, including silicates and sulfides. These results emphasize the need for laboratory experiments (*20*, *21*) to understand Stardust capture alteration of each component found in the 81P/Wild 2 sample.

Temperatures on impact were expected to reach several hundred kelvin (*22*) but exceeded 2000 K locally (*1*). Both Stardust and experimental tracks contain well-preserved sulfides and melted sulfides (~1000 K), decomposed and intermixed with melted aerogel, illustrating the compromised state of the Stardust sample and dramatic variation of thermal and shock conditions within single tracks due to capture (*4*). Given these conditions, we considered whether the GEMS-like material in Stardust tracks is cometary GEMS intermixed with aerogel. Simply diluting CP IDP GEMS with excess SiO_2 would preserve the original nonvolatile-element atomic ratios (excluding Si and O). Instead, Mg normalized by Al (Table 1), for example, is four times smaller in the GEMS-like material in Stardust. Even if there are cometary GEMS indigenous to 81P/Wild 2 in the Stardust sample, it may ultimately be impossible to unambiguously distinguish them because of their unfortunate similarity to impact-produced materials (Fig. 4). Because of their distinctive morphologies and ease of recognition, enstatite whiskers were the first crystalline silicates identified and described in detail in CP IDPs (*15*). Enstatite is a relatively robust mineral that has survived in abundance in Stardust tracks; however, no [100]*-elongated enstatite whiskers or platelets have yet been identified.

Additional CP IDP constituents underrepresented in Stardust samples are carbonaceous material and presolar grains. Refractory carbonaceous material (Fig. 1B) is rare in Stardust tracks, with abundances more typical of chondritic meteorites (*23*), whereas CP IDPs are the most carbon-rich meteoritic materials known, with 13 wt % C on average and as much as ~50% by volume (*16*, *24*). Most refractory cometary carbonaceous material should have survived, given the survival of fully stoichiometric sulfides and partial reduction of others (Fig. 4A) (*4*, *19*). Where organic material has been analyzed, D/H ratios lie well below values determined for CP IDPs (*2*). Grains of stardust identifiable by nonsolar isotopic compositions are also rare. Only one presolar grain has been confirmed so far in the Stardust sample, compared to ~8 to 10 in single CP IDPs measured recently (*2*, *9*, *11*). The low abundances of carbon and isotope anomalies, the presence of a CAI and probable chondrule fragments, and the lack of GEMS and enstatite whiskers and platelets indicate that any petrologic relationship between 81P/Wild 2 and the parent bodies of CP IDPs is at best tentative.

The mineralogical and isotopic evidence to date suggests that comet 81P/Wild 2 more closely resembles an inner solar system asteroid than an outer solar system comet with primitive unaltered dust. Ongoing studies will clarify the relationship between 81P/Wild 2 and specific class(es) of asteroidal meteorites (*25*). Accumulating evidence suggests that the Kuiper belt is populated in part by objects that either accreted closer to the Sun and subsequently migrated outward or accreted in situ from transported inner solar nebula materials (*26*). The possibility of finding some refractory component of inner solar system CAIs and chondrules in a single comet nucleus was acknowledged even before the Stardust mission (*27*). The recent discovery of main-belt comets with asteroidal orbits and comae (*28*) indicates no clear demarcation in the early solar system between asteroid- and comet-forming regions. The distinction between comets and asteroids is, in many cases, simply a matter of aging (loss of volatiles) and orbital parameters (*29*).

The nondetection to date in comet 81P/Wild 2 samples of the most abundant and most recognizable silicate materials in cometary CP IDPs, combined with low abundances of carbon and presolar grains and the presence of characteristic inner solar system refractory materials, reinforces the scientific importance of stratospheric IDP collection. All captured 81P/Wild 2 particles were modified, many severely, during abrupt deceleration into aerogel and aluminum foil (*1*, *4*). Stardust may also have collected a few contemporary interstellar dust particles from the Ulysses dust stream (*1*), but severe modification is expected for these as yet unrecovered particles, collected at about three times the 81P/Wild 2 capture speed. In contrast, the upper atmosphere has proven an ideal medium for gentle deceleration of small meteoritic particles traveling at cosmic velocities because of the gradual density gradient. CP IDPs are in continuous and inexhaustible supply, and many IDPs survive atmospheric entry with minimal thermal and shock alteration (*8*). At present, CP IDPs remain the most cosmically primitive astromaterials least altered by capture that are currently available for laboratory study and a valuable resource for understanding the origins and evolution of planetary systems.

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Supporting Online Material

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Elasticity of (Mg,Fe)O Through the Spin Transition of Iron in the Lower Mantle

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Changes in the electronic configuration of iron at high pressures toward a spin-paired state within host minerals ferropericlase and silicate perovskite may directly influence the seismic velocity structure of Earth's lower mantle. We measured the complete elastic tensor of ferropericlase, $(Mg_{1-x},Fe_x)O$ ($x = 0.06$), through the spin transition of iron, whereupon the elastic moduli exhibited up to 25% softening over an extended pressure range from 40 to 60 gigapascals. These results are fully consistent with a simple thermodynamic description of the transition. Examination of previous compression data shows that the magnitude of softening increases with iron content up to at least $x = 0.20$. Although the spin transition in (Mg,Fe)O is too broad to produce an abrupt seismic discontinuity in the lower mantle, the transition will produce a correlated negative anomaly for both compressional and shear velocities that extends throughout most, if not all, of the lower mantle.

Knowledge of the physical properties of various transition-metal oxides is crucial to interpreting the seismic structure of Earth in terms of mineralogical and compositional variations. Iron is the most abundant transition metal in Earth. In the lower mantle (which extends from the 660-km discontinuity to the core-mantle boundary at a depth of 2900 km), it is hosted by ferropericlase [(Mg,Fe)O] and silicate perovskite [$(Mg,Fe)SiO_3$]. Mineralogical models of the lower mantle indicate that ferropericlase constitutes 10 to 20% of this region by volume (*1*–*3*), which partitions iron with silicate perovskite in fractions depending on both temperature and depth (*4*–*9*). Recently, the important question of spin-pairing transitions of iron from high-spin (HS) to low-spin (LS) states in ferropericlase (*7*, *10*–*17*), affecting the lower mantle's density and seismic wave velocities, has been recognized (*11*, *12*). Because knowledge of this deep and inaccessible region is derived largely from seismic data, it is essential to determine the influence of the spin transition on elastic wave velocities at lower-mantle pressures.

In ferropericlase, the spin transition occurs without change from the NaCl crystal structure or distortion of its cubic symmetry (*11*). Nevertheless, as we show, the spin-pairing transition interval is accompanied by softening of all the single-crystal elastic moduli (c_{11}, c_{12}, and c_{44}) by up to 25% between 40 and 50 GPa. Consequent recovery of the elastic moduli between 50 and 60 GPa brings velocities close to those extrapolated from the low-pressure HS state. The elastic behavior is continuous and consistent with a macroscopic thermodynamic description of the transition, which is inherently non–first order. The observed anomalies in elastic properties of this material with ~6% iron represent a minimum effect, which would be enhanced in compositions with more iron and in the range of expected lower-mantle compositions of 10 to 15% iron.

Single crystals of $(Mg_{0.94},Fe_{0.06})O$ were loaded into the cavity of a diamond anvil cell with an argon pressure-transmitting medium. Impulsive stimulated scattering was used to measure body and interfacial acoustic velocities over a 60° range in a (100)-type plane at increments of 10° (*18*).

At lower pressures, the data (circles in Fig. 1) are in agreement with those calculated on the basis of an extrapolation of a linear fit to the elastic properties determined by Jackson *et al*. (*19*) to 20 GPa (solid lines). However, near 40 GPa, all velocities begin to decrease relative to the extrapolation and reach minima between 47 and 50 GPa. Velocities then begin to increase again and approach those of the extrapolation above 60 GPa.

All three elastic constants (Fig. 2) inferred from the acoustic wave velocities [supporting online material (SOM) text] exhibit normal behavior below 40 GPa. In the pressure regime between 40 and 60 GPa, all the c_{ij} show substantial softening and then consequent recovery relative to the linear extrapolations after passing through minima at about 48 GPa. The anisotropy parameter A [i.e., the difference between the shear moduli $c'=(c_{11}-c_{12})/2$ and c_{44}], which is equal to zero for isotropic solids, is negative at low pressure, passes through zero near 20 GPa, and continues on a smooth positive trend at higher pressure. Unlike the individual constants, no anomalous dependence is apparent in the 40- to 60-GPa regime (*20*).

The spin transition in ferropericlase is associated with a decrease in volume (*11*) that is dependent on iron concentration (x) [e.g., (*15*, *16*, *21*)]. A heuristic explanation, based on the geometry of 3*d* electronic orbitals, rationalizes a coupling of the spin transition with acoustic wave velocities. The five 3*d* electronic states for iron are divided into two e_g orbitals (spatially directed toward the neighboring oxygen anions) and three t_{2g} orbitals (spatially oriented between the neighboring oxygen anions). Occupation of the e_g orbitals (giving rise to higher electron density along the iron-oxygen bond) tends to expand the lattice. An additional lattice distortion breaks cubic local symmetry to lift the degeneracy of the e_g states (the Jahn-Teller effect). In HS ferropericlase, each

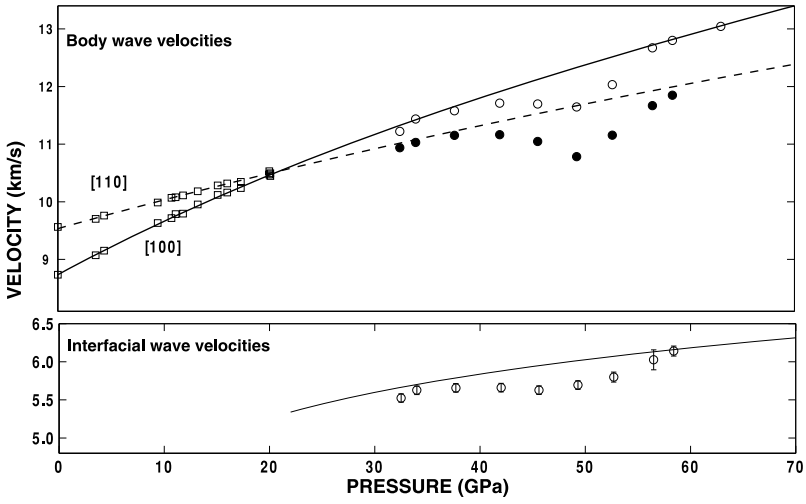

Fig. 1. Acoustic wave velocities as a function of pressure for propagation in the (001) plane of single-crystal $(Mg_{0.94},Fe_{0.06})O$ in an argon pressure-transmitting medium. Circles indicate present data acquired by impulsive stimulated scattering. Uncertainties are given by ± 2σ, where σ is the formal SE. Squares indicate data obtained by Jackson *et al*. via Brillouin scattering (*19*). Lines are calculated velocities based on linear extrapolations of the elastic moduli obtained by Jackson *et al*. (*19*). (**Top**) Body wave velocities. Solid circles and open circles are data for propagation along [110] and [100], respectively. (**Bottom**) Velocities of the wave that propagates at the interface between the sample and the pressure-transmitting medium. The interfacial wave has no dependence on direction under these conditions.

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e_g state is occupied by an unpaired electron, giving rise to antiferromagnetic coupling, an expanded lattice, and noncubic local symmetry. In the LS state, all six 3*d* electrons are contained in the three t_{2g} orbitals. Transition to the LS state is accompanied by a decrease in volume and reduction or altering of the lattice distortion. HS and LS states coexist with a statistical distribution that is dependent on pressure *P* and temperature *T*. The LS state is not favored at low pressure as a result of the exchange energy involved in pairing of electrons in the otherwise lower-energy t_{2g} orbitals. An expression for the fraction of iron cations in the LS state (*n*) can be derived through minimization of the Gibbs energy with respect to *n* (*15*). It is dependent on the enthalpy difference ($\Delta H = \Delta E + P\Delta V$, where ΔV and ΔE are the change in volume and the change in internal energy associated with the transition, respectively) between the two states

$$n = \frac{1}{1 + m(2s+1)e^{\frac{\Delta H}{kTs}}} \quad (1)$$

where *m* and *s* are the electronic degeneracy and iron spin quantum number, respectively, of the HS state, and *k* is Boltzmann's constant. Increasing pressure drives the system into the LS configuration as a result of the $P\Delta V$ energy associated with the transition (*16*). However, at finite temperature, a consequence of Eq. 1 is that the transition is non–first order. Acoustic waves, as agents of both dilatational and shear strains, couple to the spin transition if it and the consequent changes in size and geometry are fast as compared with the acoustic period. In the region of transition, a positive increment of stress will drive the system toward the LS state. In turn, this causes an increment of strain in excess of the normal elastic behavior. A softening of the associated elastic moduli thus occurs. The volume and geometric changes discussed above are at least qualitatively sufficient to account for softening of both the compressional and shear moduli.

Lin *et al.* (*11*) reported compression data to 135 GPa for ferropericlase with 17% iron in a neon pressure-transmitting medium. These data (Fig. 3) clearly show three regimes: HS behavior below 40 GPa, LS behavior above 60 GPa, and a transition regime between 40 and 60 GPa. Fourth-order finite-strain equations-of-state fits are plotted in the figure as dashed lines. As predicted by ab initio calculations (*15*, *16*), HS and LS iron have similar equations of state that are simply displaced by a ΔV of transition. A curve (depicted as the thick solid line in Fig. 3) fitting all compression data was constructed on the basis of Eq. 1 and linear volume mixing. The ab initio prediction is depicted as the thin solid line. Because ΔV is determined by the equations of state for the two spin states, a linear dependence of ΔE on pressure was adjusted to fit the compression data. The change in ΔH that was responsible for the HS-to-LS transition is principally associated with the increasingly negative contribution from $P\Delta V$ (Fig. 4). ΔE changes only modestly over this pressure regime.

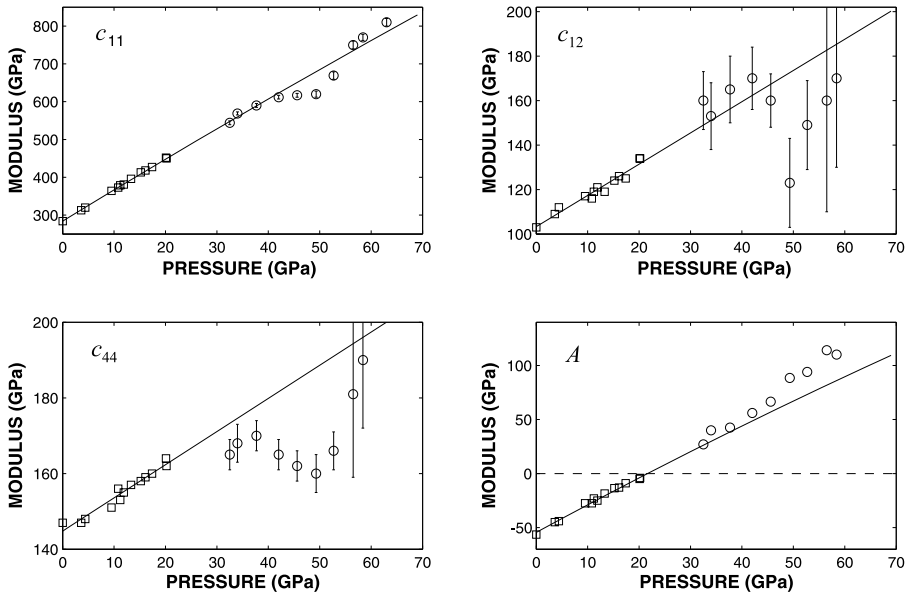

Fig. 2. Measured pressure dependence of the elastic moduli c_{ij} and anisotropy factor $A = (c_{11} - c_{12})/2 - c_{44}$. Circles indicate the present data, and squares are data of Jackson *et al.* (*19*). Lines are linear fits to the latter data. Error bars indicate two SEs obtained from fits to the measured velocities.

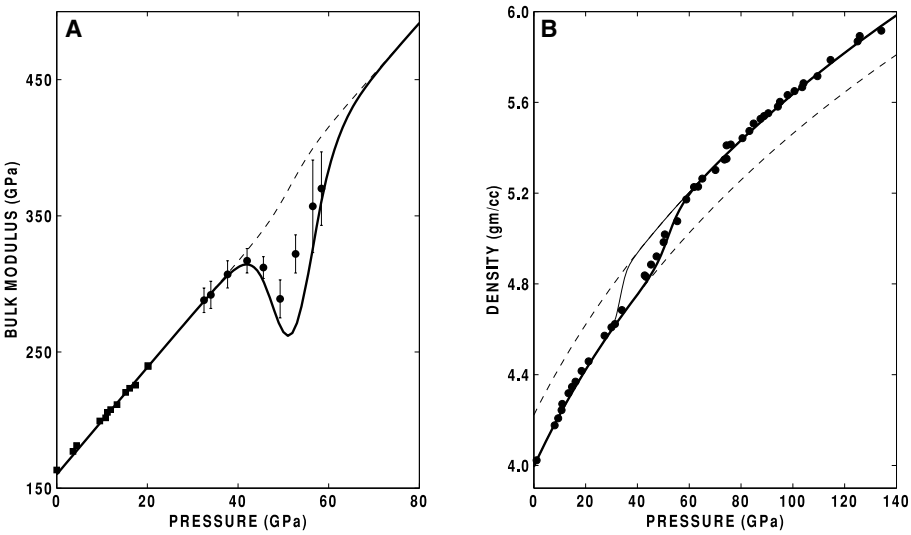

Fig. 3. (**A**) Bulk modulus versus pressure. Circles indicate present data calculated on the basis of the c_{ij} shown in Fig. 2. Squares are values calculated on the basis of the data of Jackson *et al.* (*19*). The solid line is based on a thermodynamic description of the HS-to-LS transition with parameters scaled from those that fit the compression data of Lin *et al.* (*11*). The dashed line is the average of separate equations of state for the HS and LS phases [see (B)]. Error bars indicate two SEs obtained from fits to the measured velocities. (**B**) Experimental data of Lin *et al.* (*11*) showing density of $(Mg_{0.83},Fe_{0.17})O$ versus pressure. The dashed lines represent equations-of-state (fourth-order Eulerian finite-strain) fits (*22*) to the HS (low pressure) and LS phases. The thick solid line is a fit to the data based on Eq. 1. The thin solid line is the first-principles theoretical prediction of Tsuchiya *et al.* (*15*).

In the dilute limit (noninteracting iron sites), thermophysical properties should scale linearly with iron concentration (*15*). We therefore scale terms in Eq. 1 and Fig. 4 from the $x = 17\%$ material investigated by Lin *et al.* (*11*) to our sample with $x = 6\%$. The agreement in the pressure regime of transition and degree of modulus softening suggests that the thermodynamic description is reasonable (Fig. 3). Using the same approach, we have also compared our data to the compression data obtained by Fei *et al.* (*21*) for material with $x = 20\%$ (fig. S2) in an annealed NaCl pressure-transmitting medium. Although the latter data suggest a minimum in the bulk modulus at a lower pressure of about 39 GPa, the observation of the softening, its magnitude, and the extent of pressure over which it occurs are entirely consistent with our results.

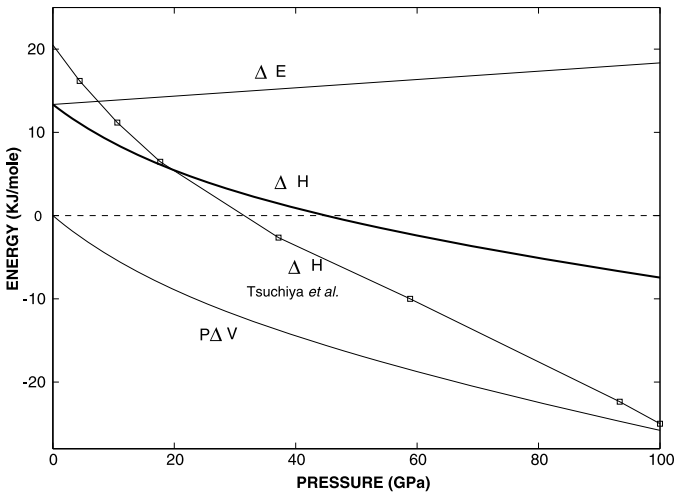

Fig. 4. HS-to-LS transition enthalpy, $\Delta H = \Delta E + P\Delta V$, and component terms, ΔE and $P\Delta V$. The thick solid line showing the enthalpy was obtained from the data of Lin *et al*. (*11*) (see text). It is a sum of the individual components shown. The line with squares is the result of a first-principles calculation by Tsuchiya *et al*. (*15*).

We have measured the elastic tensor of $(Mg_{0.94},Fe_{0.06})O$ through the pressure-induced HS-to-LS transition. We find that there is an extensive range of pressure over which all the c_{ij} exhibit an anomalous but smooth softening. By reinterpreting previously published compression data of materials with much higher iron concentrations (more representative of the lower mantle), we show that similar but even more pronounced behavior is exhibited by at least the bulk modulus. The current data show that, even at room temperature, the HS-to-LS transition in (Mg,Fe)O is not expected to result in a sudden increase in seismic velocities at any depth. Although this finding is inconsistent with the conclusions of (*11*), it is qualitatively consistent with the results of the more recent x-ray emission experiment carried out at simultaneous high pressure and temperature by Lin *et al*. (*17*), who noted that the spin transition takes place over an extended range of pressure and temperature. On the basis of our room-temperature results, this range extends from 1000 to 1500 km. At elevated temperatures and on the basis of Eq. 1, this range increases to include most or all of the lower mantle and results in a decrease in compressional and shear velocities of a few percent.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/319/5862/451/DC1
Materials and Methods
Figs. S1 and S2
Tables S1 and S2
References

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Enriched Pt-Re-Os Isotope Systematics in Plume Lavas Explained by Metasomatic Sulfides

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To explain the elevated osmium isotope (^{186}Os-^{187}Os) signatures in oceanic basalts, the possibility of material flux from the metallic core into the crust has been invoked. This hypothesis conflicts with theoretical constraints on Earth's thermal and dynamic history. To test the veracity and uniqueness of elevated ^{186}Os-^{187}Os in tracing core-mantle exchange, we present highly siderophile element analyses of pyroxenites, eclogites plus their sulfides, and new $^{186}Os/^{188}Os$ measurements on pyroxenites and platinum-rich alloys. Modeling shows that involvement in the mantle source of either bulk pyroxenite or, more likely, metasomatic sulfides derived from either pyroxenite or peridotite melts can explain the ^{186}Os-^{187}Os signatures of oceanic basalts. This removes the requirement for core-mantle exchange and provides an effective mechanism for generating Os isotope diversity in basalt source regions.

The possibility of observing the chemical signature of core-mantle interaction in magmas erupted at Earth's surface is one of the most exciting prospects in mantle geochemistry. The observation of $^{186}Os/^{188}Os$-$^{187}Os/^{188}Os$ excesses in some plume-related lavas has recently been invoked as the strongest evidence of substantial mass exchange between the Earth's core and mantle (*1*–*5*). This hypothesis has considerable consequences for the evolution of the core, specifically requiring inner core crystallization early in Earth's history. This constraint on the inner core's crystallization age is in direct contradiction of recent models of terrestrial cooling (*6*, *7*) which predict ages of core crystallization as young as 1.5 billion years (Gy) old, too late then to generate the required ^{186}Os enrichment. Further objections to the core-mantle exchange model have come from the absence of $\varepsilon^{182}W$ anomalies in the same plume-related lavas (*8*) and from new high-pressure solid metal–liquid metal highly siderophile element (HSE) partition coefficients (*9*), which predict an outer core composition that is unable to generate elevated ^{186}Os and ^{187}Os, even over several billion years (Fig. 1). With the continued finding of $^{186}Os/^{188}Os$-$^{187}Os/^{188}Os$

excesses in mantle-derived magmas, it is timely to examine other potential explanations of this signature to find a possible resolution of these contradictions.

Recycling of crustal materials such as Fe-Mn crusts, oceanic crust, or melting of a mixed pyroxenite-peridodite source (*10*–*12*) have been proposed instead of core-mantle interaction. These alternative hypotheses focus on intramantle mixing processes and have considerably different implications for the thermal and dynamic evolution of Earth. They each have weaknesses. Recycling of Fe-Mn crusts and oceanic crust were ruled out because of their variable ^{187}Os signature, their volumetrically low abundance, and their low Os contents (*1*). The mixed pyroxenite-peridodite source hypothesis is more attractive but has not been properly tested with a representative, extensive Re-Pt-Os abundance and isotopic database. Nonetheless, this hypothesis is in accord with recent geochemical and petrological studies that involve large contributions (10 to 100%) of pyroxenite-derived melts in the source of mid-ocean ridge basalts, ocean island basalts, and komatiites (*13*, *14*). Hence, more detailed documentation of pyroxenite HSE abundances and Os isotope systematics is required, especially the potential role of base-metal sulfides (BMS) in generating highly variable ^{186}Os-^{187}Os isotope systematics in prospective basalt source regions. BMS control the HSE abundance budget of the mantle [e.g., (*15*)]. These minerals are highly mobile in the mantle, being capable of metasomatizing mantle sources (*15*–*17*). They can then introduce a wide variety of Os isotope compositions and Pt/Os and Re/Os fractionations (*15*–*17*). As such, BMS may hold the key to understanding mantle ^{186}Os-^{187}Os isotope systematics.

We report $^{186}Os/^{188}Os$ and $^{187}Os/^{188}Os$ compositions (calculated and measured) together with HSE abundances for 11 pyroxenites from the Beni Bousera orogenic massif (table S1) (*18*). In addition, 20 BMS grains have also been measured from Beni Bousera pyroxenites plus eclogite xenoliths from the Mir and Udachnaya kimberlites. Beni Bousera pyroxenites are considered to be good analogs of pyroxenites present within the asthenospheric mantle because they appear to be derived from an oceanic crust protolith (*19*). They have reaction margins with the surrounding peridotites that are analogs for the hybrid sources required by melts with a substantial pyroxenite influence (*20*). Eclogite xenoliths have also been shown to have a recycled crustal origin (*21*) and have experienced long-term residence in the lithospheric mantle (*22*). Sulfides from these lithologies provide the host for most of the Os signatures and together with their low melting points provide an effective means of transferring Os isotope signatures. Because of difficulties in obtaining sufficient Os for precise analysis of $^{186}Os/^{188}Os$ ratios, especially in single mantle-derived sulfides, we model most of the $^{186}Os/^{188}Os$ compositions by assuming an age for the pyroxenites of 1.2 Gy (*18*). This age is indicated for some Beni Bousera pyroxenites by a previous Lu-Hf and Re-Os study (*19*). Although ancient, the 1.2-Gy age is somewhat younger than the suggested mean age of recycled oceanic crust residing in the convecting mantle on the basis of Pb isotopes (*23*). As such, the ranges of isotopic compositions that we report are likely conservative minima (*18*).

Beni Bousera pyroxenites show pronounced but very variable enrichment of Pt and Re over Os (Fig. 1). Their calculated (C) $^{187}Os/^{188}Os_C$ ratios (*18*) are systematically radiogenic. Their $^{186}Os/^{188}Os_C$ ratios vary over a wide range, from close to chondritic to considerably radiogenic ($^{186}Os/^{188}Os_C$ = 0.1198401 to 0.1198934). The most radiogenic $^{186}Os/^{188}Os_C$ ratios are substantially higher than the most radiogenic plume-related lava sample (Fig. 1). The measured (M) $^{187}Os/^{188}Os_M$ and $^{186}Os/^{188}Os_M$ ratios obtained for GP137 and GP251, two samples where sufficient whole-rock powder was available for analysis, confirm our calculations. In particular, GP 137 has a nonradiogenic $^{186}Os/^{188}Os_M$ signature, whereas GP 251 is radiogenic in ^{186}Os, even more so than are plume-related lavas ($\varepsilon^{186}Os$ = +0.71, compared to the most radiogenic Gorgona samples). The slight discrepancy observed between the measured and calculated isotopic ratios likely reflects the variable, inherited, radiogenic Os in the pyroxenite at the time of their formation because the Beni Bousera pyroxenites have an origin from recycled oceanic crust.

The isotopic diversity of the pyroxenites makes them attractive as potential source components for explaining lavas' ^{186}Os-^{187}Os systematics. Partial melts derived from a mantle source containing both peridotites and pyroxenites similar in HSE composition to those at Beni Bousera could reproduce the radiogenic Os isotopic composition of plume-related lavas (Fig. 2). A simple two-component bulk mixing model calculated between a present-day mantle peridotite and the two pyroxenites with the highest $^{186}Os/^{188}Os$ (GP 251 and GP 87T) indicates that a basalt containing 50 to 90% of pyroxenite-derived melt would have combined $^{187}Os/^{188}Os$ and $^{186}Os/^{188}Os$ ratios similar to the radiogenic plume-related lavas. More specifically, our calculations indicate that 60%, 70 to 75%, and 85% of pyroxenite-derived melts could explain the ^{186}Os-^{187}Os systematics of Mauna Loa, Loihi,

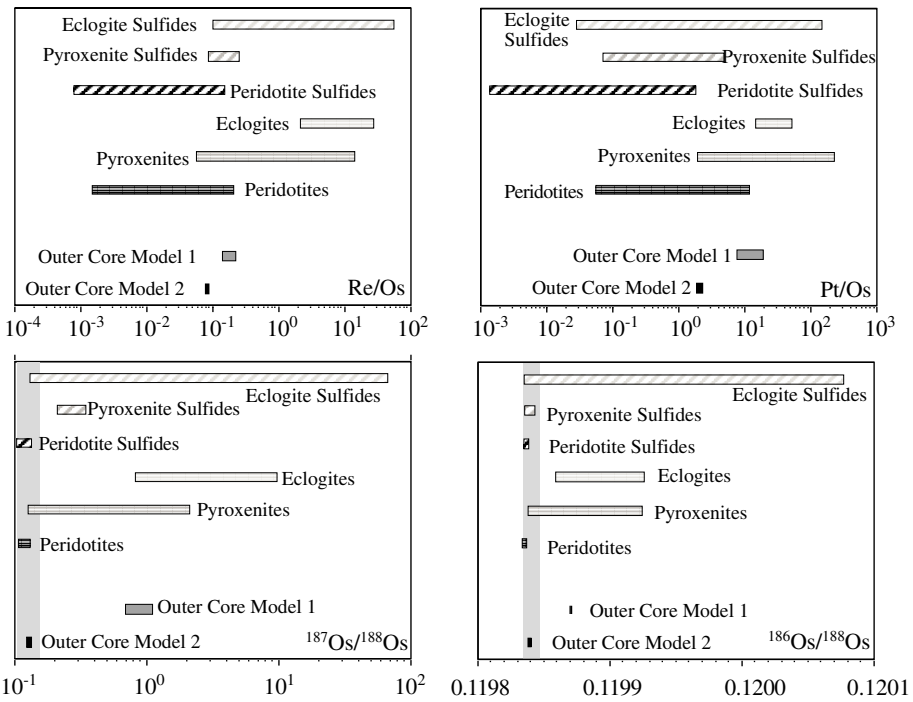

Fig. 1. Variations of Re/Os, Pt/Os, $^{187}Os/^{188}Os$, and $^{186}Os/^{188}Os$ for models of the outer core compared with measured and predicted values for whole-rock peridotites (*15*, *16*, *29*), eclogites (*22*), pyroxenites (table S1) (*19*), sulfides from eclogites and pyroxenites (table S1), and residual sulfides from peridotites (*15*–*17*). The gray field denotes Os isotopic composition of ^{186}Os-enriched plume-related lavas (*2*–*5*). The outer core model 1 is from (*4*) and assumes a 4.4- to 3.4-Gy-old inner core. The outer core model 2 was calculated using bulk core composition of (*4*), Os, Ir, and Pt metal solid/metal liquid partition coefficients experimentally obtained at 22-Gy (*9*) and a 1.5-GPa crystallization age of the inner core in agreement with Earth heat budgets (*6*, *7*). Outer core model calculations were performed assuming both linear and instant growth models for the inner core crystallization.

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and Hualalai shield volcanoes, respectively, in good agreement with the estimates made using ^{187}Os-^{87}Sr systematics (*13*). These large volumes of pyroxenite-derived melts imply 4 to 16% of recycled crust within the mantle source (*14*), in excellent agreement with the proportion of pyroxenitic material observed in subcontinental lithospheric mantle and ophiolite massifs (5 to 10% volume) (*19*).

Although the above estimates of the proportion of pyroxenite in the source of mantle-derived magmas, made on the basis of Pt-Re-Os isotope systematics, are consistent with the proportions indicated from other constraints (*13*, *14*), bulk mixing models are probably not applicable to mass balance arguments involving HSE. This is because these elements are concentrated within BMS which, during melting and mixing processes, will not behave like silicate phases. Being highly reactive and mobile trace components of mantle rocks (*15*–*17*), BMS have the ability to produce dramatic changes in HSE abundances and isotopic ratios during metasomatic events where very low mass fractions are exchanged, principally the low-temperature melting components such as BMS.

In mantle peridotites, HSE contents and $^{187}Os/^{188}Os$ ratios of the BMS vary largely at the micrometric scale (*15*–*17*) (Fig. 1). That this microscale heterogeneity extends to the pyroxenitic/eclogitic parageneses is confirmed by the wide range of HSE concentrations with Re/Os and Pt/Os ratios, spanning 0.5 to 3 orders of magnitude, within BMS from Beni Bousera pyroxenites and Udachnaya and Mir eclogites (table S1 and Fig. 1). However, in contrast to peridotite sulfides, pyroxenite and eclogite BMS systematically have radiogenic to very radiogenic $^{187}Os_C$ compositions (Fig. 1). Half the samples show subchondritic to slightly suprachondritic $^{186}Os/^{188}Os_C$ ratios (0.1198369 to 0.1198454) (table S1), whereas the rest have very radiogenic to extreme $^{186}Os/^{188}Os_C$ ratios (0.1198557 to 0.1200785). The most radiogenic $^{186}Os/^{188}Os_C$ ratios are considerably higher than the whole-rock pyroxenites or eclogites and well in excess of any modeled outer core compositions (Fig. 1). $^{186}Os/^{188}Os$ ratios even more extreme than the BMS values modeled here have been measured in Pt-rich alloys from ophiolites (up to 0.1217) (table S1) (*11*), confirming the potential of HSE carriers to generate highly radiogenic signatures within the shallow upper mantle.

During melting of a mixed pyroxenite-peridotite source, the pyroxenitic component melts first, with the resulting melts reacting with the peridotite wall-rocks (*20*). It is this reacted wall-rock that subsequently controls melt composition. During this process, sulfides, because of their low solidi, will be among the first components to be transferred into the surrounding metasomatized wall-rock. Melting of mantle peridotite that has been metasomatically enriched with HSE-rich, isotopically heterogeneous microphases such as BMS derived from pyroxenites or eclogites could explain the entire spectrum of ^{187}Os-^{186}Os variation in plume-related lavas (Fig. 2). For example, melting of a peridotitic mantle containing 1.5% of BMS similar to the two eclogite BMS M2015-3 and M2015-9, would generate partial melt with an Os isotopic composition matching the most radiogenic Gorgona komatiite samples. The amount of metasomatic BMS required is as low as 0.035 to 0.12% if the BMS are Os-rich, such as those observed in some highly metasomatized peridotites from the Kaapvaal craton (*24*) (e.g., FRB 98/6). Of course, the proportion of metasomatic sulfides is highly dependent on the assumptions made to model their Os isotopic composition. For example, the proportion of sulfides required for the mass balance is multiplied by a factor of 2 to 3 if sulfides are 500 million years (My) old but drop by a factor of 2 if the sulfides are 2 Gy old. Moreover, although the reacted peridotite composition is likely to be affected by the addition of metasomatic sulfides, especially regarding S and Pt contents (*18*), the oceanic basalts are unlikely to inherit those anomalous signatures because of the limited solubility of these two elements within silicate melts (*25*, *26*).

HSE alloys are a possible alternative to BMS being the key agent for dominating the ^{187}Os-^{186}Os source characteristics of magma source regions. HSE alloys can have extremely radiogenic $^{186}Os/^{188}Os$ and $^{187}Os/^{188}Os$ and high HSE contents (Fig. 2 and table S1) (*11*). Although these alloys mostly form in the oceanic mantle lithosphere (*11*, *27*), their very radiogenic values, such as those found here, can be explained by in-growth during crustal residence. Nonetheless, if such grains found their way back into mantle source regions through recycling of lithosphere, they are likely to dominate mantle HSE budgets and isotope systematics. Although the potential of transferring their Os isotopic signatures to partial melts is unclear because of their refractory and chemically inert nature, HSE alloy recycling in the mantle could represent another potential mechanism to diversify the Os isotopic composition of upper-mantle–derived melts worthy of further research.

We conclude that the coupled ^{186}Os-^{187}Os enrichment observed in plume-related lavas can have an upper-mantle origin related to source regions having experienced BMS metasomatism by pyroxenite and/or peridotite-derived partial melts. Addition of metasomatic sulfides to mantle peridotite is a common process in the lithospheric mantle. It has been shown to operate also in the oceanic mantle, explaining both the $^{187}Os/^{188}Os$ systematics of abyssal peridotites (*17*) and the Pd enrichment of the oceanic mantle (*15*, *16*). Sulfide metasomatism, and its resulting effects on S abundances, has been documented in veined pyroxenite-peridotite sequences (*28*), and the measurements and modeling presented here illustrate the effectiveness of the process in dominating the ^{186}Os-^{187}Os systematics of mantle rocks. Hence, the observation of coupled ^{186}Os-^{187}Os excesses in mantle-derived magmas cannot be taken to be a unique signature of core-mantle interaction.

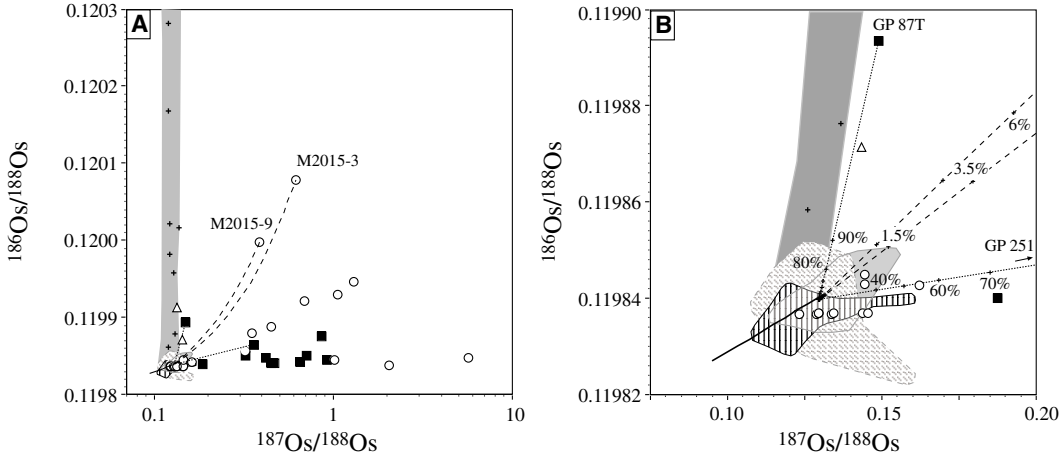

Fig. 2. (**A**) ^{186}Os-^{187}Os systematics of Beni Bousera pyroxenites (squares, predicted), sulfides from pyroxenite and eclogite sulfides (circles, predicted), Kaapvaal peridotites (triangles, predicted) (*24*), and HSE alloys from the Josephine ophiolite (dark gray field and crosses, measured). The medium gray field denotes plume-related lavas (*2*–*5*); obliquely lined field, osmiridiums (*11*); and vertically lined field, osmiridiums and chromitites (*2*, *30*). The dotted line represents the mixing line between pyroxenites GP87T and GP251 and a present-day mantle peridotite, and the dashed lines represent the mixing line between the eclogite sulfides (M2015-3 and M2015-9) and a present-day mantle peridotite. Mass of sulfides in mixture denoted in %. (**B**) is a magnification of (A) to better show the match between ^{186}Os-enriched plume-related lavas and the metasomatic sulfides to peridotite mixing trend. The *x* axis in (A) is in logarithmic units.

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Irreconcilable Differences: Fine-Root Life Spans and Soil Carbon Persistence

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The residence time of fine-root carbon in soil is one of the least understood aspects of the global carbon cycle, and fine-root dynamics are one of the least understood aspects of plant function. Most recent studies of these belowground dynamics have used one of two methodological strategies. In one approach, based on analysis of carbon isotopes, the persistence of carbon is inferred; in the other, based on direct observations of roots with cameras, the longevity of individual roots is measured. We show that the contribution of fine roots to the global carbon cycle has been overstated because observations of root lifetimes systematically overestimate the turnover of fine-root biomass. On the other hand, isotopic techniques systematically underestimate the turnover of individual roots. These differences, by virtue of the separate processes or pools measured, are irreconcilable.

Fine roots (those with diameters <2.0 mm) serve at least two roles of global importance: They act as conduits transporting carbon (C) into belowground C pools, and they acquire soil resources. Consequently, predictive models of plant function, forest nutrition, and global C cycling depend on accurate quantification of fine-root longevity and turnover rate.

Considerable effort has been expended to quantify the potential for fine roots to absorb C from the growing pool of atmospheric CO_2 and to sequester it in mineral soil. Globally, soil C pools are particularly important because they contain approximately 3.3 times more C than the atmospheric pool and 4.0 times more C than the aboveground terrestrial biomass pool (*1*–*4*). Much of the C present in soil is probably derived from fine roots (*5*).

Understanding fine-root dynamics is also critical for understanding how plants acquire water and nutrients from soil. Because most uptake occurs in roots <1 mm in diameter, fine-root pool size may limit forest productivity by limiting plant absorptive capacity. Fine roots are also the primary site of infection by mycorrhizal fungi, which influence a wide range of ecosystem properties, including productivity, biodiversity, and soil structure.

There is currently an ongoing debate on the efficacy of methods that measure C residence time in fine roots using ^{13}C-depleted atmospheric enrichment (*6*) versus methods that observe roots directly by means of microvideo cameras (minirhizotrons) (*6*–*8*). This debate has been fueled by the observation that isotope-based estimates of C residence times in fine roots are much longer (>4 years) than estimates of root longevity determined by repeated observation with minirhizotrons (<1 year) (*9*, *10*). Several sources of discrepancy between these approaches have been identified: (i) differences in the pool of roots sampled with isotope versus minirhizotron methods (*8*, *11*), (ii) the confounding effects of carbohydrate storage on depletion rates of C isotopes (*12*), (iii) the appropriateness of underlying survival functions assumed by isotope methods (*10*, *13*), (iv) overestimation of turnover rate because of using median longevity as a surrogate for mean longevity in minirhizotron studies (*11*), and (v) slow return to equilibrium root dynamics after the installation of minirhizotron access tubes (*14*).

Although technical issues inherent to isotopic and minirhizotron methods have led to disparate conclusions about fine-root dynamics, arguments regarding the validity of these methods skirt the issue that multiple belowground processes require characterization and, although related, may best be measured with different approaches. In this study, we set out to reconcile measures of fine-root C pool dynamics derived with isotopic methods and fine-root dynamics obtained from minirhizotrons. First, we assess the relative magnitudes of several sources of measurement error associated with isotope and minirhizotron approaches; second, we attempt to quantify the differences between C residence and individual root-dynamic–focused studies. We used survival analysis to examine the root dynamics in the CO_2-enriched plots at the Duke University free-air CO_2 enrichment (FACE) facility (*15*). The longevity of 2181 individual roots, with diameters <2 mm, was recorded over 8 years from repeated video images; 64% of these roots were followed until senescence and death. The remainder were alive at the end of the experiment and were treated as right-censored in survival analyses. We then compared our results to estimates of root turnover derived using isotopic techniques from the same forest plots, published by Matamala *et al.* (*6*).

Previously published isotopic estimates of turnover for this forest (*6*) have been criticized on

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the basis of speculation that they were derived using an inappropriate survival model (*7*). It was suggested that a more appropriate model would lower longevity estimates (*10*). We used direct measurement of individual root life spans to identify the most appropriate model and then applied this model to previously published isotopic data for these plots (*6*). For root survival, comparison among several models indicated that a log-normal survival model fit best with a Bayesian information criterion (BIC) score of 3248.12 as compared to BIC scores for Weibull and exponential distributions of 3463.17 and 3463.18, respectively. Although the log-normal model fit root survival best, reanalyzing published isotopic data using this model instead of the exponential model used previously failed to increase the earlier estimate of turnover rate. The model invoked to estimate turnover of fine roots, in this case, did not explain the difference in turnover rates obtained with isotope and minirhizotron techniques.

Projections of the longevity of roots, or the C they contain, assume that belowground processes are in equilibrium. Insertion of minirhizotron tubes is a necessary disturbance. It has been unclear to date how rapidly disturbed soil will return to equilibrium conditions or if this even occurs during the course of a given minirhizotron study. We took both a meta-analysis and a single-study approach to estimate this rate. Data from seven minirhizotron studies that were at least 2 years in duration were used to estimate root turnover (per year) from yearly production and the average yearly standing crop, using a flux approach (*15*, *16*). We then took the reciprocal of fine-root turnover to estimate mean longevity for each year of each study. Although heterogeneity among studies was observed for absolute longevity, longevity estimates increased significantly with increases in study duration (Fig. 1). For instance, fine-root longevity increased from an average of 0.7 year in minirhizotron studies conducted over 1 year as compared to 1.0 year for studies conducted over 3 years, an increase of over 40%. We also examined this process for individual root survival at the Duke FACE site by directly measuring root life spans and estimating the mean longevity of roots initiated in each of the years of the study. We observed that roots initiated in early years exhibited lower mean life span and a return to equilibrium by year three (Fig. 2). Based on this return to equilibrium, we separated the individual roots into those initiated during the first 3 years (pre-equilibrium) and those initiated in the last 5 years (post-equilibrium). The longevity of fine roots established during the pre-equilibrium period was 50% shorter as compared to the longevity of roots that developed during the post-equilibrium period (Fig. 1 and Table 1). This result indicates that short-duration experiments, characteristic of most minirhizotron studies, may have contributed to inflated estimates of fine-root turnover rates.

Another important distinction between the isotopic and minirhizotron approaches involves units of measurement. Whereas isotopic methods are based on mean residence time of fine-root C in units of biomass, most minirhizotron experiments report turnover of individual roots themselves. Because smaller-diameter, more numerous roots turn over more quickly than larger-diameter, less numerous roots, treating all roots equally could contribute to inflated C turnover rate estimates when using minirhizotrons. Moreover, studies conducted with minirhizotrons often use median root longevity values as a surrogate for mean longevity. This assumption also contributes to underestimations of root longevity, because root survival functions are positively skewed (Table 1) (*6*, *7*). To alleviate these sources of error, we applied parametric survival regression, based on units of root volume as a surrogate for root biomass, to estimate mean longevity for roots initiated in the last 5 years of the study. These survival curves were compared to those of individual roots and the

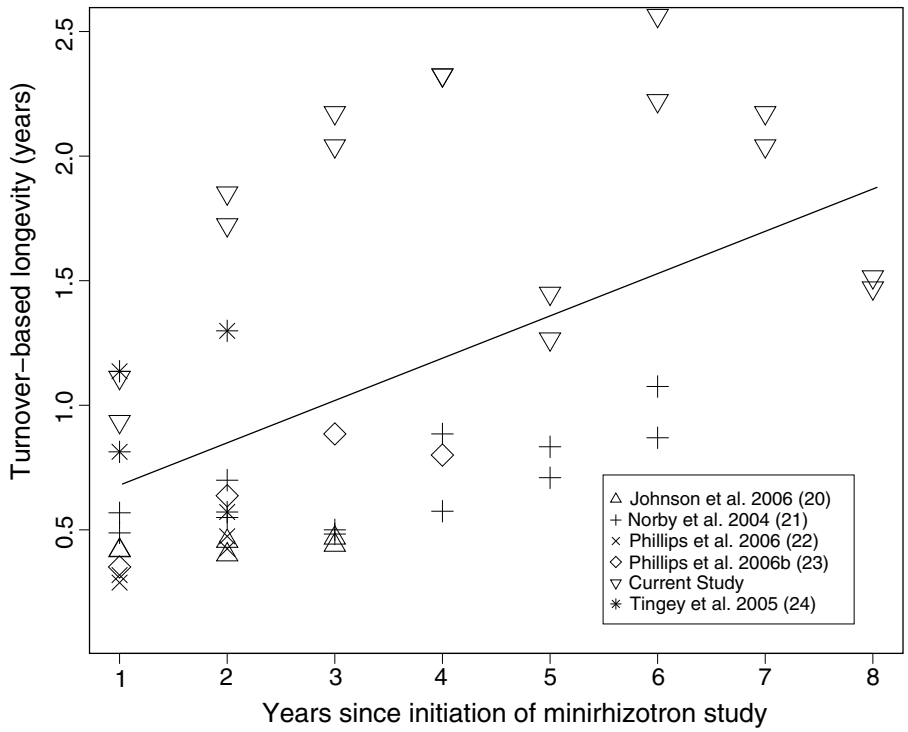
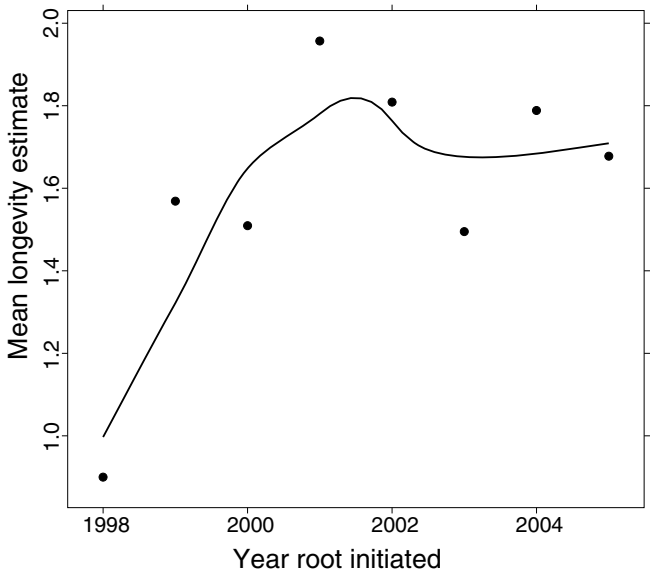


Fig. 1. Estimates of fine-root longevity from root turnover measurements as a function of the number of years since the initiation of the minirhizotron study. Turnover values were derived from annual production divided by average annual standing crop (*14*). Analysis of covariance supports the hypothesis that longevity estimates increase over time ($P < 0.001$) and that there is little support for the hypothesis that this slope differs among studies ($P = 0.97$). This analysis explains 81% of the variation in longevity estimates. The solid line represents a best linear fit to these data overall ($y = 0.51 + 0.17x$). Numbers in parentheses are reference numbers.

Fig. 2. Estimates of the mean longevity of individual fine roots appearing at different times during the Duke FACE study. Mean estimates are derived from parametric regression of fine-root survival times, which also indicated significant variation among survival curves stratified by year of initiation ($P < 0.0001$, log-normal distribution of survival times). The solid line represents a loess fit to mean longevity for visualization.



residence time of C in the same plots (Fig. 3). We found that estimates based on the longevity of individual roots lead to a 50% exaggeration of fine-root biomass turnover rate.

It has been suggested that the finest roots are not adequately sampled by destructive soil coring because of the difficulty of extracting them from the cores (*17*). Missing the smallest (≤0.3 mm) and most ephemeral roots could bias isotopic measures of longevity upward (*11*). We tested the potential for this sampling bias to contribute to the underestimation of fine-root turnover using the isotopic approach. Our results suggested that poor sampling of these shorter-lived smaller roots may significantly affect isotope-based C longevity estimates, because such sampling in our data increased the longevity of biomass in the soil (fig. S2) (*15*).

In this study, we have eliminated several biases proposed to explain the divergence in fine-root longevity common to isotope- versus minirhizotron-based methods. Because we controlled for time, place, and several technical assumptions of both isotope and minirhizotron analyses, the remaining differences result from several factors that we cannot control. The isotopic technique fails to account for heterogeneity in fine-root life span: The longevity of fine roots increases considerably with increasing soil depth and diameter and with branching order, and may be influenced by herbivory (*18*, *19*). Interpretations of isotopic results could also be confounded if some proportion of new fine roots is constructed using C recycled from senescing tissues or storage pools (*12*). For example, some time may pass from the time when C is acquired through photosynthesis and the time when new roots are constructed from that C in spring. Furthermore, recycling of old C to support growth of newer roots could also cause individual C atoms to persist in the fine-root pool much longer than the individual roots themselves. Finally, the difficulty of obtaining the smallest roots from soil cores in isotopic analyses will bias isotope-based estimates of longevity upward.

Characterizing the persistence of C and the longevity of roots is not redundant; each is essential for understanding ecosystem function. Quantifying belowground C pools is also critical for parameterizing global C cycle models. Our results indicate that applying the median longevity of individual roots in short-term minirhizotron studies underestimated residence time of fine-root biomass by over 300% as compared to mean longevity of fine-root volume (biomass) derived from a long-term experiment. This suggests that previous estimates that fine-root turnover represents 33% of annual global net primary production (*9*) are probably unrealistically high. However, understanding soil C pools is of limited use in understanding ecosystem function in other ways. C pools may provide a gross reflection of root biomass, but because these pools are somewhat insensitive to the dynamics of the smallest roots, they provide little information on water and nutrient uptake potential, the demography of plant modules, or relative investments in absorption versus transport.

Unfortunately, the behavior of the soil C pool and the dynamics of the fine-root pool have often been conflated in the literature (table S1) (*15*). Misapplying the results of an isotope-based estimate of C persistence will underestimate root turnover rate by 60% and, more importantly, underestimate the rate at which the finest roots—the location of interaction between plants and soil—are produced. Conversely, misapplication of minirhizotron results, particularly those derived from short-term experiments, will dramatically overestimate the rate at which fine-root turnover transfers C into the soil. These methods are both fundamentally irreconcilable yet complementary.

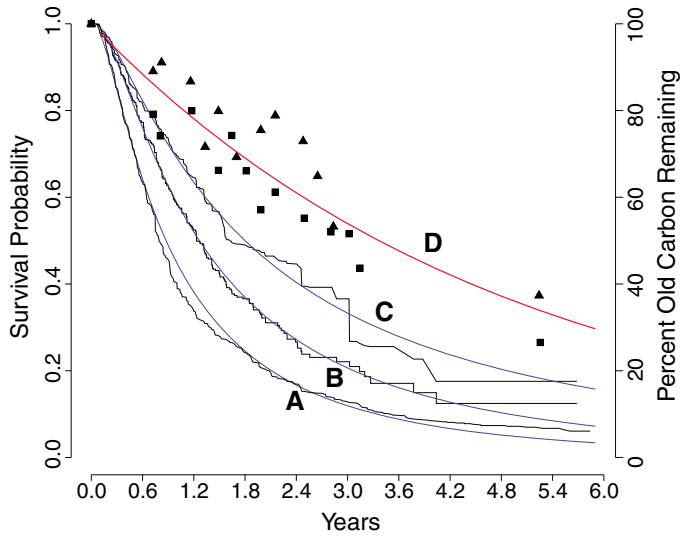


Fig. 3. Survival curves derived from individual roots from minirhizotron images, compared to isotopic estimates of C persistence. Points refer to estimates of percent of C remaining for roots <1 mm in diameter (squares), or between 1 and 2 mm in diameter (triangles), or between 2 and 5 mm in diameter (circles) [from Matamala *et al*. (*6*)]. Black curves represent Kaplan-Meier estimates of survival functions, whereas blue lines represent the best fit of a log-normal survival function to each empirical curve. Each corresponds to the survival of roots ≤2 mm in diameter. (**A**) Survival of individual roots estimated from roots initiated in the first 3 years of the study. (**B**) Survival of individual roots estimated from the last 5 years of the study. (**C**) Survival of individual units of root volume (biomass) estimated from the last 5 years of the study. (**D**) Best exponential fit to the percent of C remaining (*6*).

Table 1. Estimates of mean life span for individual roots and root biomass from parametric survival regression of root life spans compared to C residence time from a ^{13}C study. CI, confidence interval.

Survival type	Time period	Mean life span in years (95% CI)	Median life span in years (95% CI)
Individual roots	Pre-equilibrium	1.51 (1.45, 1.59)	0.79 (0.75, 0.86)
Individual roots	Post-equilibrium	2.21 (2.08, 2.36)	1.23 (1.12, 1.41)
Biomass (volume)	Pre-equilibrium	2.61 (2.42, 2.81)	0.93 (0.92, 1.04)
Biomass (volume)	Post-equilibrium	3.24 (3.01, 3.49)	1.64 (1.55, 2.04)
Isotope-based	-	5.3 (4.8, 5.8)	-

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Adaptive Plasticity in Female Mate Choice Dampens Sexual Selection on Male Ornaments in the Lark Bunting

Alexis S. Chaine[1,2]* and Bruce E. Lyon[1]

Theory on the evolution of ornamental male traits by sexual selection assumes consistency in selection over time. Temporal variation in female choice could dampen sexual selection, but scant information exists on the degree to which individual female preferences are flexible. Here we show that in lark buntings sexual selection on male traits varied dramatically across years and, in some cases, exhibited reversals in the direction of selection for a single trait. We show that these shifts are probably because of flexibility in mate choice by individual females and that they parallel shifts in the male traits that predict female reproductive success in a given year. Plasticity in choice and concomitant reversals in mating patterns across time may weaken the strength of sexual selection and could maintain genetic variation underlying multiple sexual ornaments.

Sexual selection for exaggerated secondary sexual traits arises from two different mechanisms that result in correlations between male traits and mating success—male-male competition for access to females and female mate choice (*1*, *2*). These mechanisms can be difficult to disentangle (*3*), but direct female choice for extravagant male traits has been shown in many taxa (*2*). Ornament evolution via female choice requires that females prefer an extreme expression of a male trait, that trait preferences are concordant among females in a population, and that these preferences are fairly consistent across time (*4*, *5*). Changes in the ecological or social environment could favor flexibility in female preferences (*6*, *7*), but information about the temporal consistency of female choice is currently lacking (*6*, *8*). Plasticity in female preferences could have major effects on the strength and outcome of sexual selection (*9*) and, potentially, could slow trait exaggeration (*10*).

We investigated the dynamics of pairing patterns and mate choice in the lark bunting, *Calamospiza melanocorys,* a migratory songbird breeding on the short-grass prairie of Colorado. Sexual selection is potentially strong in lark buntings, because many males fail to attract a social mate [~45% of territorial males (*11*)] because of a male-biased breeding sex ratio coupled with social monogamy and because extra-pair paternity is common [25% of young and 47% of broods (*11*)], but variable among males. To assess the dynamics of sexual selection, we studied five independent male plumage traits and three measures of size (Fig. 1)—body color, proportion of black versus brown feathers separately on the rump and the rest of the body, wing patch size, wing patch color, body size, beak size, and residual mass (*12*). To examine sexual selection on these male traits, we assessed both the social pairing success of color-banded males in each breeding season, as well as their total annual fitness, using microsatellite parentage analysis (*12*).

In territorial birds, it can be difficult to distinguish between direct female choice for male traits and female choice for territory features correlated with male traits (i.e. male dominance badges). Male lark buntings, however, are only weakly territorial until mate acquisition, at which time the territory is no longer defended nor respected by other males [new males begin displaying on the former territory (*11*)]. Display territories are not used for feeding by either males or females (including offspring feeding), but females nest near or on the display territory, so we quantified territory quality as the density of woody shrubs available for use as nest cover (*12*).

In each of the 5 years of this study, plumage or size characteristics of males were associated with total male fitness [number of within- and extra-pair fledglings sired (*12*) (Fig. 2)], which indicated significant potential for sexual selection on those male traits. However, a significant effect of year on the traits that correlate with male fitness indicated that the specific traits under sexual selection varied among years [according to a generalized linear model (GLM): full model $F_{3,380} = 5.19$, $P = 0.001$; effect of year: $F_{4,379} = 7.52$, $P < 0.001$ (*12*)]. Examination of these patterns revealed dramatic changes across years in the suites of traits that predicted male fitness, and moreover, no two years showed similar patterns of male traits associated with fitness (Fig. 2).

We observed two distinct types of change in the pattern of selection on male traits across years. First, some male traits were under strong selection in some years, but showed very weak selection or no selection in other years [beak size and rank body color (Fig. 2)]. Cubic splines illustrate the specific form and intensity of phenotypic selection on male traits each year (*12*, *13*) and demonstrate the occurrence of this on-off pattern of selection

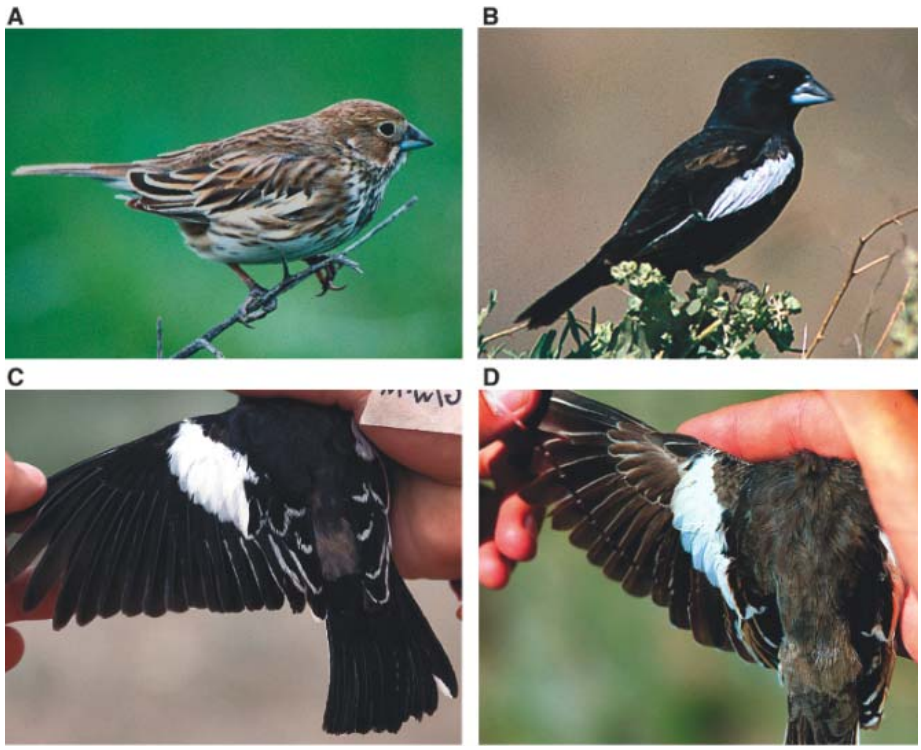

Fig. 1. Plumage traits of lark buntings. (**A**) Females are brown with dull white wing patches, whereas (**B**) males are generally black, but often have patches of brown feathers that vary in size and distribution (note patch above wing). The conspicuous white wing patches vary in both size and color among males and are both larger and brighter than those of females. There is considerable variation in color between (**C**) black males and (**D**) gray ones. Likewise, the proportion of dark versus brown feathers varies among males on both the body [(C) versus (D)] and rump (C) relative to other body parts.

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for several traits [colored lines (Fig. 3)]. Similar effects have been shown in other species (*14*, *15*). Second, three traits—body size and the percentage of black feathers on both the rump and the rest of the body—showed a positive association with male fitness in 1 year and a negative association in another year. These reversals from positive to negative selection gradients were significant (GLM: year × body size $F_{4,379} = 3.56$, $P = 0.007$; year × rump% $F_{4,379} = 3.25$, $P = 0.012$; year × body% $F_{4,379} = 3.08$, $P = 0.016$) and indicate that dramatic shifts in selection occur across years [(Fig. 2) and colored lines in (Fig. 3)]. The reversals in selection on male traits we document here provide a sexual selection parallel to oscillating natural selection described for Darwin's finches (*16*).

To understand the underlying cause of variable selection on male traits, we investigated a key component of male fitness: acquisition of a social mate. The general pattern of selection on male traits through mate acquisition (Fig. 4) was similar to overall selection on male traits (Fig. 2)—there was a significant association between male traits and mate acquisition, but the traits of successful males varied across years [GLM: full model $F_{3,380} = 10.22$, $P < 0.001$; effect of year: $F_{4,377} = 4.13$, $P = 0.002$; (*12*)]. Some traits were under selection because of mate acquisition in some years but not others (percentage black feathers on the body, beak size, and residual mass). Two traits—wing patch size and rank body color—showed changes in the direction of selection across years (GLM: year × wing patch size $F_{4,415} = 3.24$, $P = 0.012$; year × rank color $F_{4,415} = 3.29$, $P = 0.011$). A randomization test (*12*) indicated a close correspondence between the traits under selection because of total fitness and those under selection because of mate acquisition [Fig. 2 versus 4, $P < 0.001$, (*12*)]. The striking similarity in patterns of selection on male traits through total male fitness and through mate acquisition occurs because the majority of offspring are sired within the social pair [75% (*11*)] and suggests that across-year variation in social mating success is a major driver of variable selection on male traits.

Several observations suggest that temporal fluctuations in social mating patterns are more likely to be because of changes in female choice for male traits than changes in traits that influence competition among males for high-quality territories that females might choose. First, territory quality (*12*) was never associated with mate acquisition [i.e., was not selected by Akaike's Information Criterion (AIC) models for all years combined or for any individual year; partial $P > 0.2$ in all cases] and was therefore removed from all selection models. Second, we determined whether traits previously found to be important to male-male competition (*11*) differed across years in their importance as dominance signals. We did this using both observational and experimental methods, but in no case did the male traits associated with social dominance change across years in a manner that could explain the dynamic patterns of mate acquisition we describe here

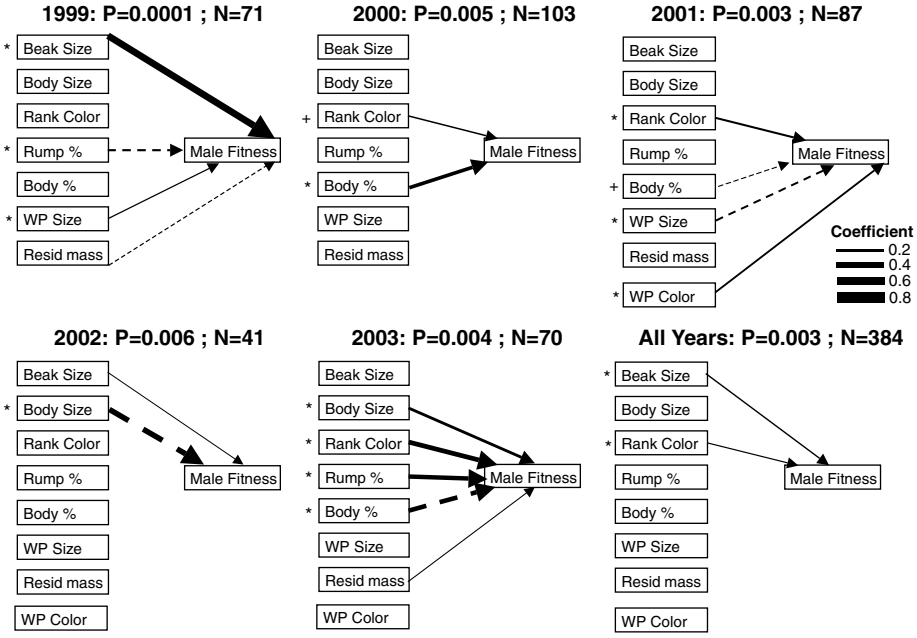

Fig. 2. Male traits associated with total male fitness (number of sired within and extra-pair chicks that fledged) show dramatic across-year variation. Year, *P* value, and sample size from the final GLM (*12*) are above each diagram. Thickness of arrows between traits and fitness indicate the partial correlation coefficient (selection gradient). Dashed and solid arrows are negative and positive relationships, respectively. Traits include three morphometric measures (beak size, body size, and residual mass) and five plumage measures: body feather color (rank color), percentage black feathers on the rump (rump%) and the rest of the body (body%), wing patch size (WP size), and wing patch color (WP color). Partial effect in GLMs designated as $*P < 0.05$, $+P < 0.1$.

(*12*). Furthermore, the level of male aggression in response to a standardized stimulus did not differ across years, which suggested that the intensity of male-male competition did not vary across years (*12*).

Two lines of evidence indicated that population-level changes in female mate choice across years were because of plasticity in individual female preferences across years rather than age-related or other demographic shifts (*12*). Females that were observed in 2 or more years and that did not stay with the same social mate (*12*) were used to estimate the degree of individual consistency [repeatability, r_t (*17*)] in mate choice (19 females whose mates were also caught: 17 in 2, 1 in 3, and 1 in 4 years). Mate choice (traits of her chosen mates) was not significantly repeatable across time (repeatability: all traits df = 2.2,19, $r_t < 0.18$; $P > 0.2$), which suggests substantial plasticity of female choice. Indeed, most females showed considerable change in the traits of their mates across years (fig. S1). Changes in the mate choice decisions of individual females will only sum to population-level dynamic sexual selection if most females show similar patterns of plasticity and response, a pattern that implicates the influence of external factors such as the social or ecological environment (*18*, *19*).

We investigated the possibility that plasticity in choice is adaptive because it allows a female to choose a male or territory character that will maximize her fitness in each year. This hypothesis predicts that females target male or territory characters that predict fitness benefits to them in a given year, that different traits serve as fitness indicators in different years, and that changes in female preference across years correspond nonrandomly with the changes in fitness-indicator traits. In most years, one or more male traits were correlated with nesting success (a measure of female fitness, fig. S2) making them potential indicator traits, and different traits were predictors of nesting success in different years (fig. S2). Randomization tests determined that there were significantly more matches than expected by chance between the traits of males chosen by females and the male traits associated with nesting success within years [four of seven male traits correlated with nesting success were also preferred by females, $n = 76$ total trait-year possibilities, $P = 0.005$; see (*12*)]. This result suggests that flexible female choice enables females to track temporal variation in the traits that predict enhanced nesting success. However, it remains unknown whether the specific traits we measured or correlates of those traits are the actual targets of female choice (*20*).

Sexual selection by female choice requires that the cumulative effects of female preferences be fairly consistent over time (*1*, *2*), and models of sexual selection with consistent choice predict extreme exaggeration of male traits (*4*, *5*). However, if female choice varies across years, phenotypic selection for male trait exaggeration could be dramatically reduced or even eliminated, as has been suggested for temporal variation in natural selection (*21*, *22*). We investigated the

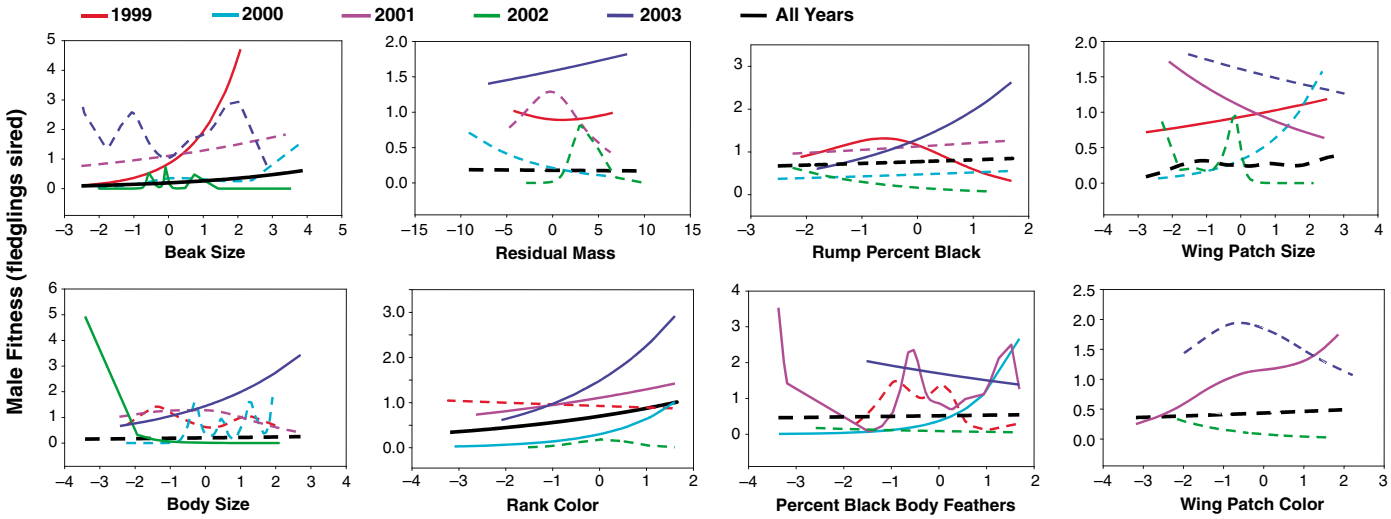

Fig. 3. Cubic splines reveal the dynamic nature of selection on male traits because of male fitness (number of fledglings sired within pair and extra-pair) across years. Colored splines represent selection on male traits in a given year; black splines represent selection in all years combined. Wing patch size and the percentage of black feathers on both the rump and rest of the body show marked reversals in the direction of selection, whereas rank body color and beak size show consistent positive relationships in all years. Solid lines depict traits that entered into selection models [models and *P* values in (Fig. 2); see (*12*)] for that year (or all years), whereas dashed lines were not significant. Only rank color and beak size show significant selection in the analysis using data from all years combined.

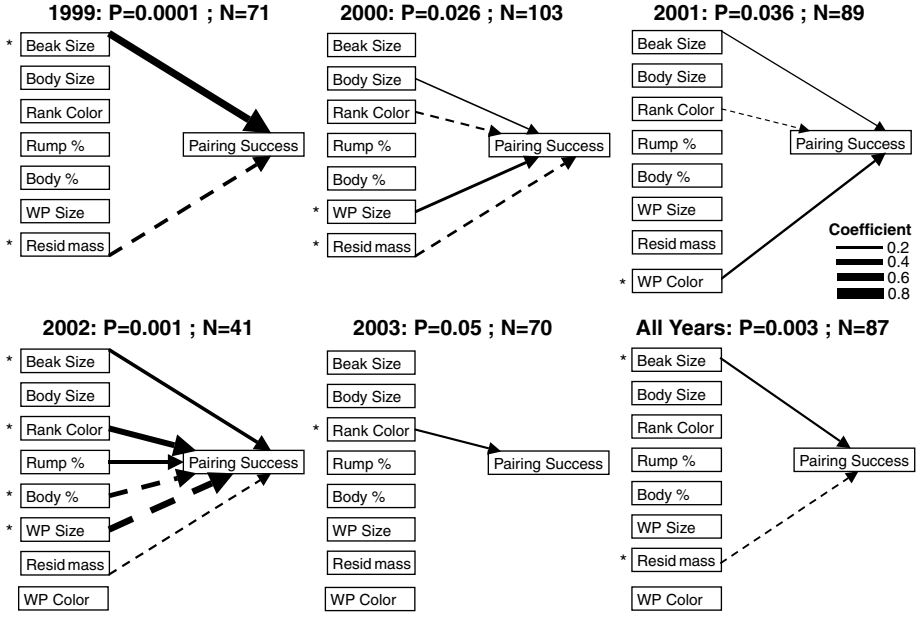

Fig. 4. Male traits associated with pairing success (mated or not mated) differ dramatically across years, presented as in (Fig. 2). Traits include three morphometric measures (beak size, body size, and residual mass) and five plumage measures: body feather color (rank color), percent black feathers on the rump (rump%) and rest of the body (body%), wing patch size (WP size), and wing patch color (WP color). Partial effect in GLMs designated as $*P < 0.05$.

impact of temporal scale on phenotypic selection by comparing analyses from individual years to an analysis of data combined across years [e.g. (Fig. 2)]. For most traits, phenotypic selection of all years combined was weak and only two traits—beak size and rank body color—were under significant selection as determined by overall male fitness patterns (Fig. 2). A similar pattern can be seen in selection on male traits through female choice of a social mate (Fig. 4). The striking effect that temporal scale has on the intensity and pattern of sexual selection can be seen by comparing selection splines on individual male traits from each year separately with those from all years pooled [colored versus black lines (Fig. 3 and fig. S3)]. By examining years separately, a very different picture of selection on male traits and female mate choice emerges from the standard approach obtained by summing across years. In lark buntings, selection on male traits is often strong within years, dynamic across years, but weak or nonexistent over a 5-year period.

Which time scale is the most appropriate for understanding sexual selection? We suggest that a longer time frame is most appropriate for predicting male trait evolution because annual male fitness measures used to estimate short-term sexual selection are unreliable when selection fluctuates across years. Short-term studies may thus prove insufficient for correctly understanding the strength and direction of sexual selection in species with variable sexual selection and flexible mate choice. In contrast, a short time frame is essential for understanding selection on female mating preferences. Only by examining female choice patterns within years was it possible to discover flexibility in choice and show the adaptive benefits of flexible choice to females.

Plasticity in female preferences has several implications for the process of sexual selection, the evolutionary dynamics of exaggerated traits, and the evolution of female choice itself. As a parallel to natural selection under variable environmental conditions, flexible female choice and dynamic sexual selection could make assessment of selection and predictions for male trait evolution unreliable (*22*) and may also provide a mechanism for the preservation of genetic variation in traits (*23*). In addition, most models of sexual selection assume that the evolution of exaggerated traits is stabilized by the costs that exaggerated traits incur (*5*, *24*). In taxa with flexible female preferences, however, choice itself may result in stabilizing selection on exaggerated traits. Finally, flexible female choice may provide an explanation for the evolution and maintenance of multiple male ornaments. Flexible choice should allow a female either to choose a mate that best complements her needs in a given year, where such needs change, or to track the best signals

when signal content changes over years because of changes in the physical or social environment. When females vary their preferences across years, the expression of more than one quality by a male would give him a mating advantage across breeding seasons by providing broad appeal under unpredictable breeding conditions. Under this scenario, selection should favor the evolution of new indicator traits that prove useful to females in some years and maintain existing multiple signals despite countervailing costs. Variation in female preferences may provide explanations for what is currently considered noise [e.g., unexplained variance, (*8*); low repeatability, (*25*, *26*)] in female choice. Testing for and incorporating temporal flexibility in female choice has the potential to greatly alter our perspectives on the process of sexual selection and trait exaggeration.

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Supporting Online Material

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Materials and Methods
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Figs. S1 to S4
References

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Control of Genic DNA Methylation by a jmjC Domain–Containing Protein in *Arabidopsis thaliana*

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Differential cytosine methylation of repeats and genes is important for coordination of genome stability and proper gene expression. Through genetic screen of mutants showing ectopic cytosine methylation in a genic region, we identified a jmjC-domain gene, *IBM1 (increase in bonsai methylation 1)*, in *Arabidopsis thaliana*. In addition to the ectopic cytosine methylation, the *ibm1* mutations induced a variety of developmental phenotypes, which depend on methylation of histone H3 at lysine 9. Paradoxically, the developmental phenotypes of the *ibm1* were enhanced by the mutation in the chromatin-remodeling gene *DDM1* (*decrease in DNA methylation 1*), which is necessary for keeping methylation and silencing of repeated heterochromatin loci. Our results demonstrate the importance of chromatin remodeling and histone modifications in the differential epigenetic control of repeats and genes.

Genomes of vertebrates and plants contain a substantial proportion of transposons and repeats (*1*). These potentially deleterious sequences are cytosine-methylated and inactivated (*2*, *3*) to form heterochromatin (*4*, *5*). Methylated heterochromatin, especially when dispersed within gene-rich regions, has the potential to spread by self-reinforcing mechanisms (*6*, *7*) to flanking cellular genes and disrupt their expression. Mechanisms that confine the methylated regions remain enigmatic, despite their importance in maintaining the integrity of large genomes with a high proportion of dispersed transposons. Here, we identify a new pathway that excludes cytosine methylation from genic regions by histone modification and chromatin remodeling, thus ensuring proper plant development.

In the flowering plant *Arabidopsis thaliana*, and in plants in general, cytosine methylation is found in both CG and non-CG contexts. In *Arabidopsis*, methylation at CG sites is maintained by the DNA methyltransferase MET1, whereas methylation at non-CG sites requires the DNA methyltransferase CMT3 (*8*–*12*). Non-CG methylation is also controlled by methylation of histone H3 at lysine 9 (H3mK9) and by the RNA interference (RNAi) machinery (*13*–*16*). DDM1, a chromatin-remodeling adenosine triphosphatase, is involved in maintenance of both CG and non-CG methylation (*17*–*19*). Mutations in *MET1* and *DDM1* also result in a variety of developmental abnormalities by inducing heritable changes in other loci (*8*–*10*, *20*, *21*). One of the *ddm1*-induced abnormalities, called *bonsai* (*bns*), is caused by epigenetic silencing of a gene encoding a homolog of a cell cycle regulator, *APC13* (*22*). The silencing of this gene, *BONSAI* (*BNS*), is associated with spreading of methylated heterochromatin from a flanking LINE retroelement (*22*). This LINE functions as methylated heterochromatin, which has a potential to spread to the flanking *BNS* gene (Fig. 1A).

To explore the mechanisms that exclude genic cytosine methylation in wild-type plants, we used methylation-sensitive restriction enzymes to screen a mutagenized population for individuals with *ibm* (*increase in BONSAI methylation*) phenotype (*23*). One of them, *ibm1*, is described in this report. The *IBM1* gene (*At3g07610*) was identified by a map-based approach (*23*). The original *ibm1-1* mutant has a base substitution causing an amino acid substitution ($Gly^{672} \rightarrow Glu$). We subsequently tested three additional *ibm1* alleles carrying T-DNA insertions and verified that these independent alleles also caused DNA hypermethylation of the *BNS* gene (Fig. 1B).

The *BNS* sequence was hypermethylated in the first generation in which the *ibm1* mutant allele became homozygous (Fig. 1B). This feature was different from the *BNS* hypermethylation in the *ddm1* mutant, which is slow and detectable only after several generations of self-pollination in the mutant background (*22*). Bisulfite sequencing revealed that cytosine methylation occurred at the *BNS* gene in *ibm1* and that non-CG sites are the main targets of the *BNS* methylation (Fig. 1C and table S1). Unlike *ddm1*, the *ibm1* mutation did not affect methylation in repeat

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sequences, such as centromeric satellites or 5*S* rDNA (fig. S1). These features suggest that low-copy sequences are the primary target of the *IBM1* gene function.

In addition to cytosine hypermethylation at the low-copy *BNS* locus, *ibm1* plants exhibited a variety of developmental abnormalities (Fig. 2 and table S2). The morphological phenotypes become apparent in the F_3 generation. Most of the *ibm1* plants formed small, narrow leaves and exhibited arrested flower development and reduced fertility (Fig. 2, A to C, and table S2). Homozygous *ibm1* plants produced few viable seeds, whereas seed set in heterozygous *IBM1/ibm1* was normal (Fig. 2D and table S3), indicating that the seed phenotype depends on the parental sporophytic genotype rather than the genotype of seed or gametophyte. Silencing of the *BNS* gene alone cannot account for the pleiotropic phenotypes exhibited by the *ibm1* mutation; knockdown of *BNS* transcripts by RNAi results in the *bonsai* phenotypes but not the other phenotypes found in the *ibm1* mutants, such as leaf deformation, abnormal flower, and reduced fertility (*22*). Multiple target loci seem to mediate the developmental defects of the *ibm1* mutations, suggesting a general role of IBM1 in the control of genome integrity.

Several considerations suggest that IBM1 might affect DNA methylation through H3mK9. The *IBM1* gene encodes a jmjC (Jumonji C) domain–containing protein in the JHDM2 family, which is constituted of demethylases of H3mK9 (Fig. 1D and fig. S2) (*24*, *25*). The Jumonji domain of IBM1 shows conservation of amino acid residues for Fe(II) and α-ketoglutarate (αKG) binding that are critical for H3K9 demethylase activity (fig. S2B) (*25*). In addition, H3mK9 is known to direct cytosine methylation by CMT3 at non-CG

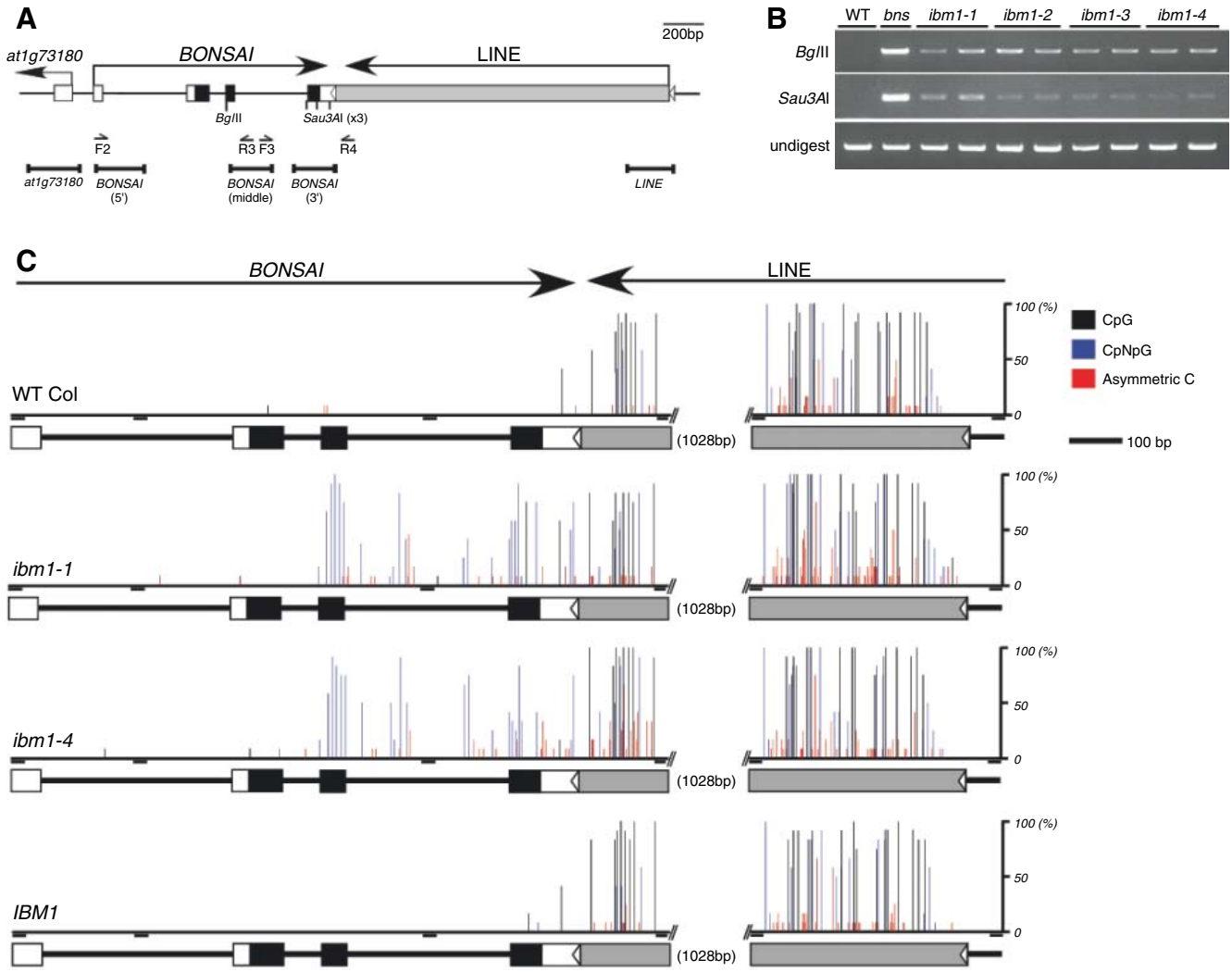


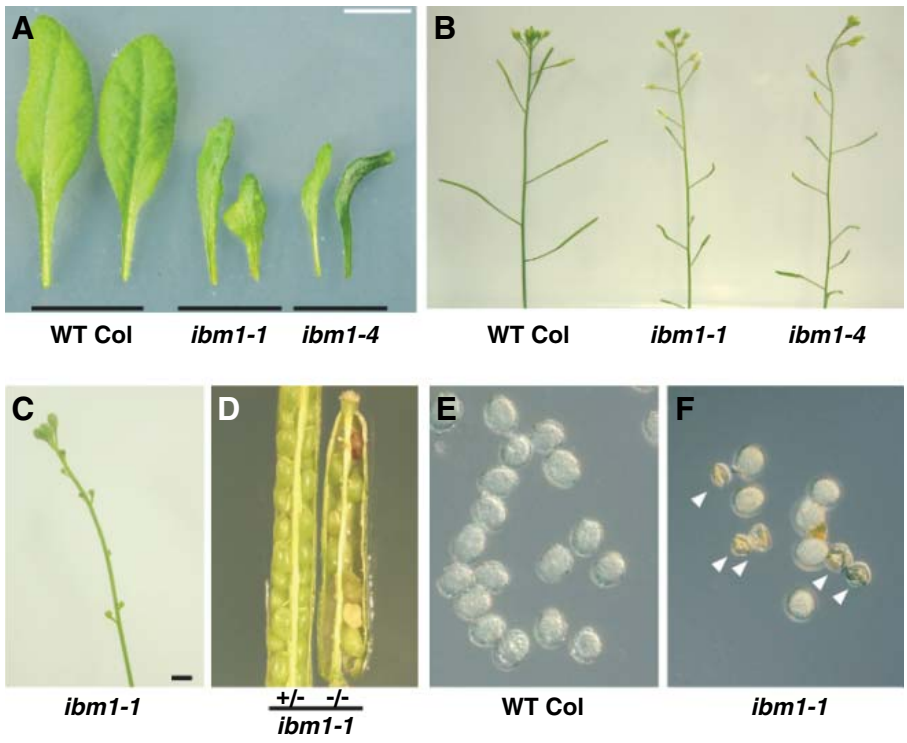
Fig. 1. Identification of *ibm1* (*increase in BONSAI methylation 1*). (**A**) Structure of the *BONSAI* (*BNS*) locus. Exons of the *BNS* gene are shown by boxes with the coding region in black and the untranslated regions in white. The gray box shows the LINE. (**B**) Methylation of the *BNS* gene in the *ibm1* mutant detected by methylation-sensitive restriction digestion. Four alleles of the *ibm1* mutants are shown, together with wild-type Columbia (Col) and the *bns* epigenetic mutation (*22*). Genomic DNA was digested by Bgl II or Sau3A I and was subsequently amplified by the polymerase chain reaction (PCR). (**C**) Bisulfite analysis of the *BNS* locus in the *ibm1* mutants. The percentage of methylated cytosine is indicated by vertical bars (black, CG; blue, CNG; red, asymmetric cytosine). (**D**) A schematic representation of structure of *IBM1* gene and IBM1 protein. T-DNA insertions are shown by white triangles and the *ibm1-1* base substitution by an asterisk.

sites (*13*, *14*). We therefore hypothesized that the hypermethylation of the non-CG sites at the *BONSAI* locus in the *ibm1* mutants is mediated by ectopic H3mK9 accumulation. In fact, chromatin immunoprecipitation experiments revealed that the H3mK9 level in the *BONSAI* locus increased in the *ibm1* mutant, especially in the 3′ region near the LINE (Fig. 3A), which correlates with cytosine methylation at non-CG sites there (Fig. 1C).

To test whether the increase in the H3mK9 level is responsible for the ectopic DNA methylation and developmental defects, we examined the effect of a mutation in the H3K9 methylase gene *KYP/SUVH4* on the *ibm1* mutant. Figure 3B shows that the *kyp/suvh4* mutation suppressed the hypermethylation phenotype of the *ibm1* mutation, suggesting that H3mK9 mediates the hypermethylation. The hypermethylation was also suppressed by a mutation in the non-CG methylase *CMT3* gene (fig. S3A). In addition to suppression of the hypermethylation, both the *kyp/suvh4* and *cmt3* mutations suppressed all of the detectable developmental phenotypes of *ibm1*, such as leaf deformation, abnormal flowers, pollen defects, and reduced fertility (Fig. 3, C to E, and tables S2 and S3), demonstrating that these diverse developmental defects are also mediated by ectopic deposition of H3mK9 and non-CG methylation.

The *ddm1* mutation results in cytosine hypomethylation and derepression of transposons and repeats. Paradoxically, the *ddm1* mutation also induces hypermethylation at some low-copy loci, such as *BNS* and *SUPERMAN* (*22*, *26*). To see whether the hypermethylation effect of the *ddm1* mutation overlaps with that of *ibm1*, we generated double mutants of *ddm1* and *ibm1*. The *ddm1 ibm1* double mutants showed strong enhancement of the developmental phenotypes (Fig. 4), with small leaves, slow growth, and complete sterility. These results suggest that the effects of the *ddm1* mutation overlap with that of the *ibm1* mutation. Although *ddm1* single mutants exhibited *BNS* hypermethylation and other developmental phenotypes only after repeated self-pollinations (*20*–*22*), the effect of the *ddm1* mutation in the *ibm1* mutant background was apparent in the first generation (Fig. 4), which suggests that the role of the *DDM1* gene in low-copy regions may be more important than previously thought. Although the *ddm1* mutation resulted in loss of H3mK9 in repeated sequences, overall level of H3mK9 was not severely affected (*27*). In the *ddm1* single mutant, its effect on the H3mK9 in genic regions may be compensated by the *IBM1* gene function.

We have shown that the IBM1 and DDM1 proteins, by repressing ectopic non-CG methylation in genic regions, are required for normal *Arabidopsis* development. Neither the *kyp* nor the *cmt3* single mutant shows developmental phenotypes (*11*–*14*), possibly because the primary target of H3K9 methylation and non-CG methylation is nongenic sequences in wild-type plants (*28*). In the *ibm1* mutant background, however, the H3mK9 and non-CG methylation machinery has pronounced effects on *Arabidopsis* development. Non-CG methylation and CG methylation are both important for silencing the repeats and transposons (*28*, *29*). At the same time, cellular genes need to be protected from the spreading of methylated heterochromatin. Coordination of the cytosine methylation in repeats and genes, through histone modifications and chromatin remodeling, will likely have an important impact on the genome integrity.



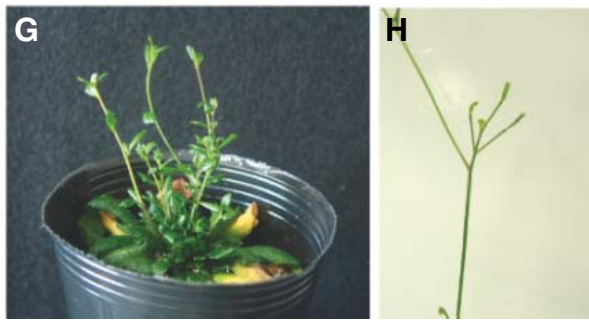


Fig. 2. Developmental abnormalities of the *ibm1* mutants. (**A** to **C**) Phenotypes of rosette leaves (A), inflorescence (B), and flowers (C) in wild-type (WT) Col, *ibm1-1*, and *ibm1-4* plants. (**D**) Abnormal seed development in an *ibm1-1* mutant (–/–) compared to an *IBM1/ibm1-1* heterozygote (+/–). (**E** and **F**) Pollen grains of WT Col (E) and *ibm1-1* (F). Arrowheads indicate degenerated pollen grains. (**G** and **H**) Plants showing *bonsai* (*bns*)–like phenotype found in *ibm1-4* (G) and *ibm1-1* (H). All the *ibm1* mutant plants were homozygous for two generations (F_3) except those shown in (G), which were homozygous for three generations. Scale bars, 1 cm (A), 2 mm (C).

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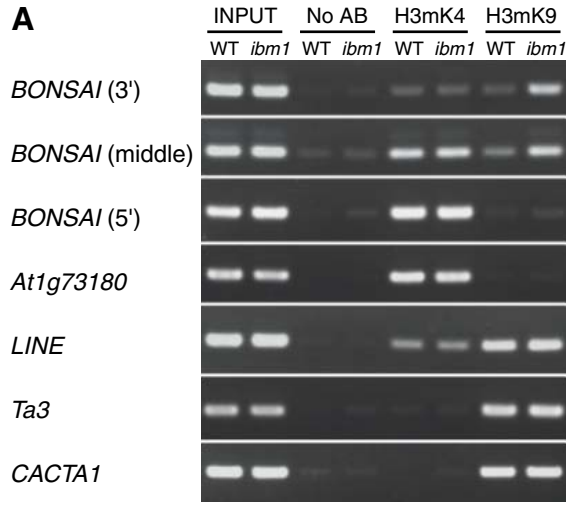

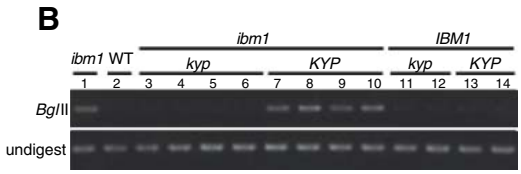

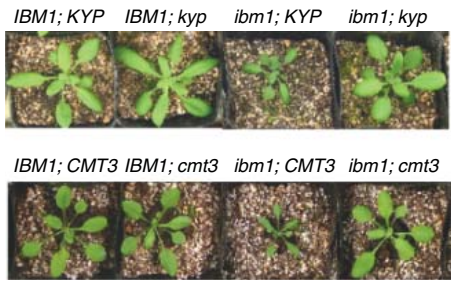

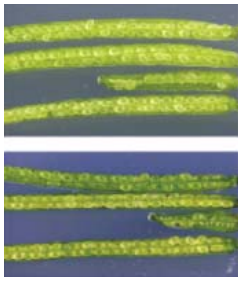

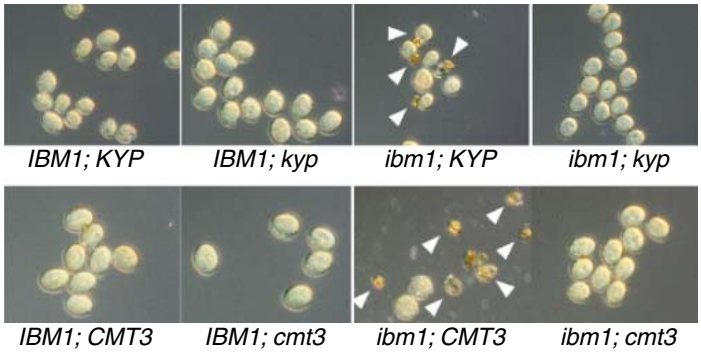

Fig. 3. *ibm1* phenotypes depend on H3K9 methylation. (**A**) Histone modification of wild-type Col (WT) and the *ibm1-4* mutant detected by chromatin immunoprecipitation (IP). INPUT is the sample before IP; No AB denotes samples after IP procedure without antibody. H3mK4 and H3mK9 are samples after IP with monoclonal antibodies against H3 with dimethylation at the corresponding lysine. Amplified regions around the *BONSAI* locus are indicated in Fig. 1A. A flanking gene *at1g73180*, LINE downstream of *BNS*, and *Ta3* and *CACTA1* transposons in other loci are used for controls. Serial dilution of the INPUT before the PCR showed that the amount of the chromatin used here was almost identical in the wild type and the *ibm1* mutant (not shown). Three independent preparations of the samples from different individuals gave essentially the same results. (**B**) The *kyp* mutation suppressed the *BNS* hypermethylation phenotype of the *ibm1* mutant. Lanes 3 to 14 show plants homozygous for the indicated genotype segregating in self-pollinated progeny of an *IBM1/ibm1-4 KYP/kyp* double heterozygote. (**C**) Abnormal leaf phenotypes in 3-week-old plants. More plants are shown in fig. S3B. (**D**) Reduced fertility phenotype. (**E**) Pollen defect phenotype. Plants shown in (C) to (E) are F_3 generation, as in fig. S3B. Phenotype scoring of all the families is shown in tables S2 and S3.

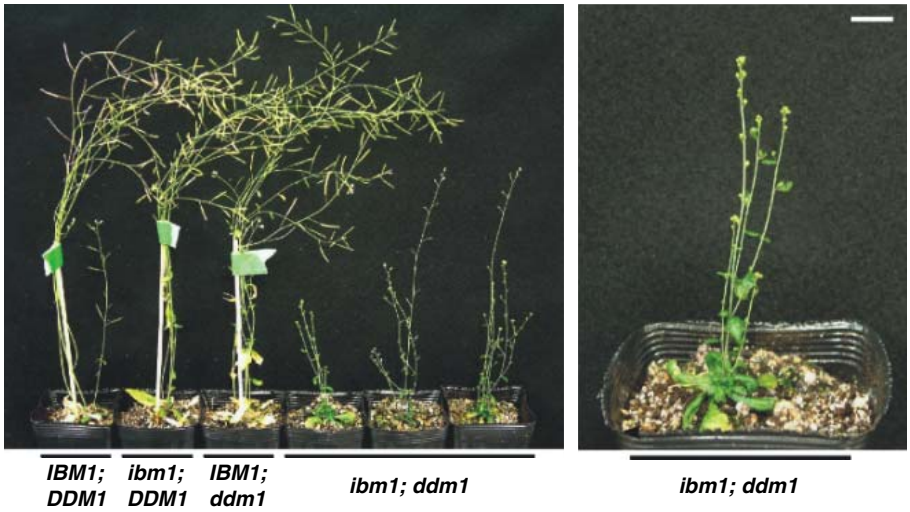

Fig. 4. Developmental phenotypes of the *ibm1* mutation are enhanced by the *ddm1* mutation. This panel shows F_2 homozygotes segregating in self-pollinated progeny of an *IBM1/ibm1-4 DDM1/ddm1-1* double heterozygote. This double heterozygote was derived from a cross between *IBM1/ibm1-4* and *DDM1/ddm1-1* backcrossed repeatedly to remove any heritable effect of the mutations (*20*). Six-week-old plants are shown. Developmental abnormalities in the *ibm1* single mutants were still mild in the segregating population. Within 189 plants in the F_2 segregating population, all 12 *ddm1/ddm1 ibm1/ibm1* plants exhibited the phenotype as shown in this figure; such a severe phenotype was not found in any of the other 177 plants, which includes 31 *ddm1/ddm1 IBM1/–* plants and 31 *DDM1/– ibm1/ibm1* plants. Scale bar, 1 cm.

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Concurrent Fast and Slow Cycling of a Transcriptional Activator at an Endogenous Promoter

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For gene regulation, some transcriptional activators bind periodically to promoters with either a fast (~1 minute) or a slow (~15 to 90 minutes) cycle. It is uncertain whether the fast cycle occurs on natural promoters, and the function of either cycle in transcription remains unclear. We report that fast and slow cycling can occur simultaneously on an endogenous yeast promoter and that slow cycling in this system reflects an oscillation in the fraction of accessible promoters rather than the recruitment and release of stably bound transcriptional activators. This observation, combined with single-cell measurements of messenger RNA (mRNA) production, argues that fast cycling initiates transcription and that slow cycling regulates the quantity of mRNA produced. These findings counter the prevailing view that slow cycling initiates transcription.

Transcriptional activators bind to the promoters of specific genes, leading to recruitment of RNA polymerase and mRNA synthesis. During this process, some transcriptional activators bind transiently, cycling on and off the promoter within seconds. These observations of fast cycling have directly challenged the conventional view of a stable transcriptional complex. However, fast cycling has only been detected on artificial gene arrays composed of hundreds to thousands of tandemly repeated, synthetically engineered genes (*1*–*4*). Studies using endogenous genes have not detected fast cycling, instead observing stable binding of a transcriptional activator to its promoter (*5*, *6*). Thus, it is uncertain whether fast cycling occurs on endogenous promoters.

We investigated fast cycling with use of the endogenous yeast *CUP1* gene, which exists naturally as a small tandem array of ~10 copies (*7*). The transcriptional activator Ace1p binds to the *CUP1* promoter in the presence of copper and induces transcription (*8*). Fusion of three copies of the green fluorescent protein (GFP) to the carboxy terminus of Ace1p yielded a fully functional, copper-sensitive activator (fig. S1C). This Ace1-GFP (Fig. 1A) enabled visualization of the *CUP1* array in live cells: Upon copper induction, two bright spots appeared in diploid nuclei (Fig. 1B) and one bright spot in haploid nuclei, whereas no comparable spots were seen with a *CUP1* deletion (fig. S1A). The spots colocalized with a chromosomal marker inserted 7 kb downstream of *CUP1* (fig. S1B), confirming that the Ace1-GFP spots marked the *CUP1* locus.

By using a laser focused on the *CUP1* locus, we permanently photobleached Ace1-GFP molecules and then measured the rate of fluorescence recovery after photobleaching (FRAP). Slower fluorescence recoveries reflect longer residence times of the bleached molecules, indicative of more stable binding. For Ace1p at *CUP1*, complete fluorescence recovery occurred within 2 min after the photobleach (Fig. 2A). This indicates a more stable and specific binding of Ace1p at *CUP1* than has been observed for Ace1p at nonspecific sites in the yeast nucleus, where complete FRAP recoveries required only about 1 s (*9*). The ~2-min recovery at *CUP1* is similar to but somewhat slower than that observed by FRAP for fast cycling of other transcriptional activators at synthetic promoters (0.3 to 1 min) (*1*–*4*) but is substantially faster than the slow cycling times of 15 to 90 min detected by chromatin immunoprecipitation (ChIP) at other endogenous promoters (*10*–*14*). These results demonstrate that fast cycling can occur at an endogenous promoter.

It is not known whether slow cycling is a slower version of fast cycling (*15*) or whether fast and slow cycling are distinct events that can coexist (*16*). The functions of fast and slow cycling are also uncertain; however, it has been argued that fast cycling reflects transient interactions of the activator with the promoter that do not lead to mRNA synthesis, whereas slow cycling reflects stable interactions of the activator with the promoter that do lead to mRNA synthesis (*16*, *17*).

With use of ChIP, we found evidence for a slow increase followed by a slow decrease in Ace1-GFP occupancy at the *CUP1* promoter (Fig. 2B). This behavior corresponded to the first of three ~40-min slow cycles of Ace1-GFP binding to *CUP1* as detected by time-lapse microscopy of either single live cells (fig. S2B) or populations of fixed cells (Fig. 2C). This slow cycle was uncoupled from the cell cycle because cells at different cell-cycle stages exhibited syn-

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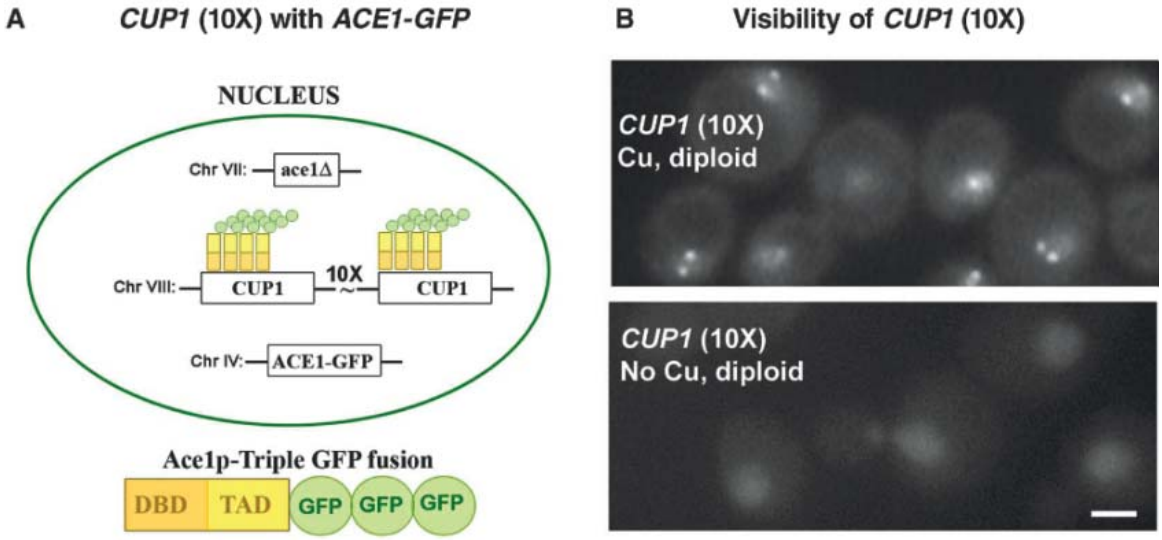
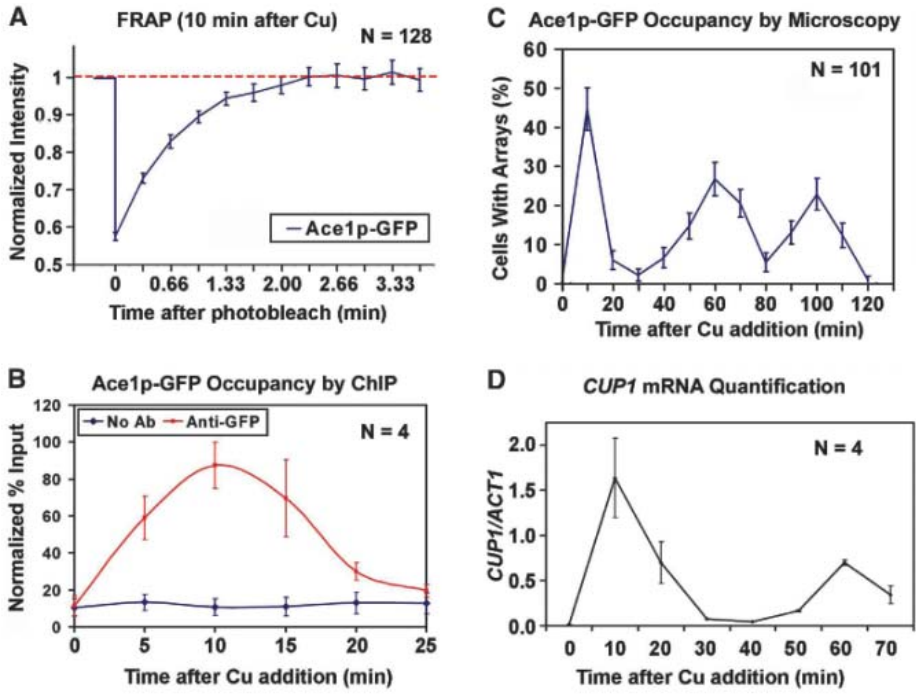


Fig. 1. Visualization of Ace1p binding to *CUP1* promoters. (**A**) Schematic of the engineered strain. Chr indicates chromosome; DBD, DNA binding domain of Ace1p; and TAD, transcriptional activation domain of Ace1p. (**B**) Live cell images illustrating appearance of the array after copper induction. Scale bar indicates 2 μm.

chronous Ace1p oscillations at *CUP1* (fig. S3). Furthermore, the slow cycle was not produced by oscillations in the concentration of Ace1p because Ace1p amounts in the nucleus remained fairly constant over the 40-min cycle (fig. S4). Oscillation in Ace1p binding to the *CUP1* promoter was paralleled by an oscillation in mRNA synthesis (Fig. 2D), suggesting that the oscillation in activator binding was functionally coupled to transcription. Together these observations demonstrate that fast and slow cycling of a transcriptional activator can coexist at the same promoters.

The general interpretation of slow cycling has been that it arises from transcriptional activators that remain bound to the promoter for most of the slow cycle (*10*–*14*, *16*, *17*) (Fig. 3A). If so, then these more stably bound molecules should not be released during the 2-min FRAP measurement, and consequently fluorescence will not recover completely to its original value (Fig. 3C). The Ace1p FRAP at *CUP1* recovers to 100% with an SEM of 4% (Fig. 2A). Thus, at most 4% of the 40 Ace1p binding sites at the 10 *CUP1* promoters (i.e., 1 to 2 molecules) can be stably bound.



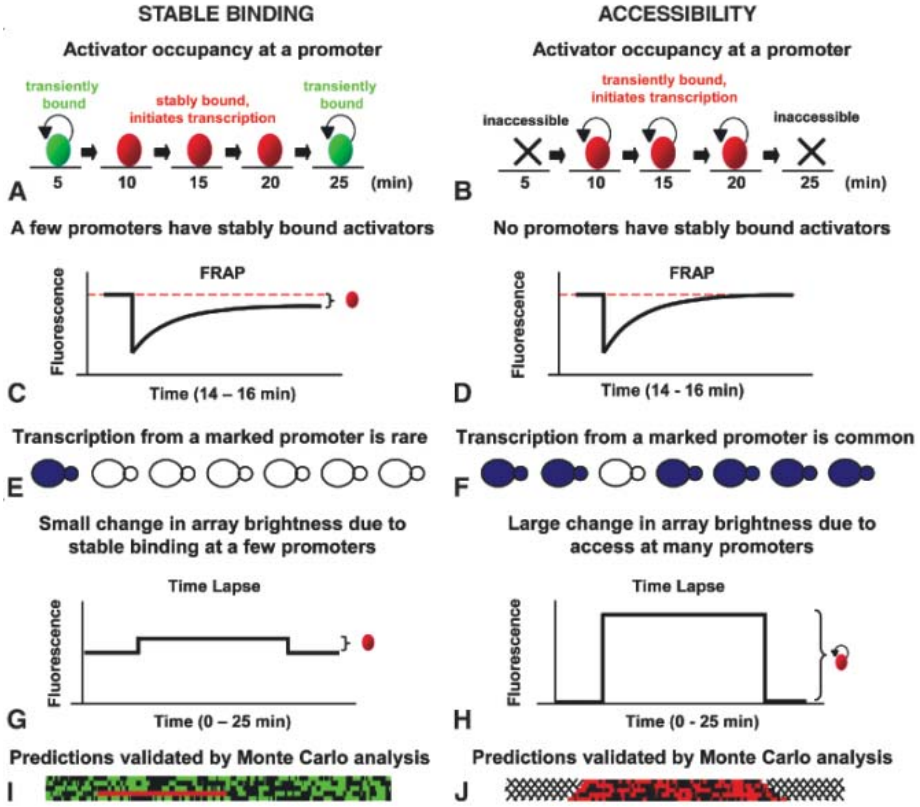


Fig. 2. Fast and slow cycles both occur at *CUP1*. All error bars indicate SEM. (**A**) Averaged FRAP curves from the *CUP1* array at 5 to 15 min after copper induction reveal a fast cycle of transcriptional activator occupancy. See fig. S5 for an example of image data. The FRAP curve recovers to 100 ± 4% (average ± SEM of the last five time points). Note that because FRAP curves are collected around the peak of the slow cycle, the recovery curve plateaus instead of being modulated by the superimposed slow cycle. *N*, number of individual FRAP curves. (**B**) ChIP on the *CUP1* array reveals a slow cycle of transcriptional activator occupancy. Shown is the quantification of four time-lapse ChIP experiments that were averaged by normalizing each time lapse such that its peak % input was 100%. See fig. S2A for an example of the ChIP raw data. (**C**) At least three slow cycles of Ace1p binding to the *CUP1* promoters were detected by counting the number of visible *CUP1* arrays in cells fixed at different time points after copper induction (see fig. S2C for representative images). (**D**) RT-PCR shows that transcriptional output from *CUP1* mirrors the slow cycle oscillation in Ace1p binding. Each measurement has been normalized by the expression level of the *ACT1* gene, which does not change in response to copper.

Fig. 3. Two models for slow cycling. In stable binding, the slow cycle arises from activators (ovals) that remain at the promoter (flat line) for an extended period (**A**). FRAP performed on an array of promoters (**C**) yields a curve that plateaus below its starting intensity (red dotted line) because stably bound molecules are not replaced during the 2-min experiment. The deficit in the final recovery level [the immobile fraction, bracket in (C)] equals the fraction of stably bound activators at the array, which must be small to match the experimental FRAP data (Fig. 2A). This small fraction is also reflected in the predicted small number of cells that produce transcript from a single, marked promoter [blue cell in (**E**)] and in the predicted small change in array intensity over 25 min [bracket in (**G**)]. In accessibility, the slow cycle arises from promoters that become accessible (**B**) to transiently bound activators (ovals with arrows). There are no stably bound activators, so the FRAP curve recovers to its starting intensity (**D**), consistent with the experimental FRAP data (Fig. 2A). Both the predicted number of cells that produce transcript from a single, marked promoter [blue cells in (**F**)] and the predicted change in array intensity over time [bracket in (**H**)] are determined by the number of promoters that become accessible, which must be large to match the experimental data (Fig. 4, A and B). Model predictions were validated by Monte Carlo simulations [examples in (**I**) and (**J**); see figs. S7 and S8 for details].

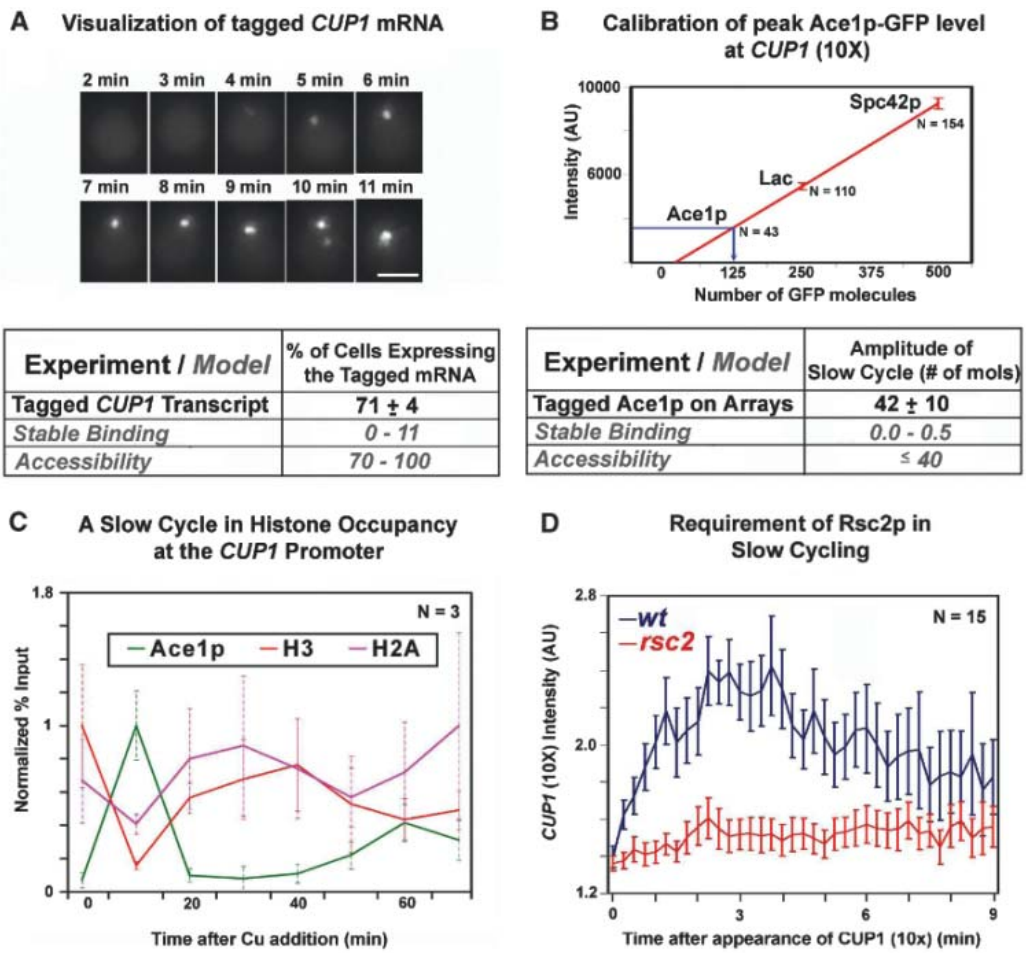
If stably bound, slow-cycling molecules initiate transcription (*16*, *17*), then only 1 to 2 of the 10 *CUP1* genes should produce transcripts (Fig. 3E), with chance determining in each cell which of the 10 array genes happen to be transcribed. This predicts that a specific gene in the array should produce transcripts in 10 to 20% of the cells. To test this, we inserted 24 binding sites for the bacteriophage MS2 coat protein into 1 of the 10 *CUP1* genes in the array and then detected its mRNA production by using a GFP-tagged form of the MS2 coat protein (*18*). Summed over 24 cells, tagged mRNA amounts mirrored the reverse transcription polymerase chain reaction (RT-PCR) data for the first 17 min after copper induction (fig. S8A) but then declined more slowly than the RT-PCR data, probably because degradation of the tagged mRNA was hindered by binding of the GFP-tagged coat proteins. We therefore restricted our measurements of tagged mRNA to the first 15 min of the slow cycle, at which time 71% of the cells showed mRNA production from the tagged *CUP1* gene (Fig. 4A). Thus, transcription from a single gene in the array is not a rare event, directly contradicting the prediction that only 1 or 2 of the 10 promoters should be capable of mRNA synthesis if the slow cycle arises from the recruitment and release of stably bound molecules.

As an independent test of whether there were only one or two stably bound molecules per *CUP1* array, we measured the amplitude of the Ace1p-GFP slow cycle. This amplitude corresponds to the peak number of stably bound molecules (Fig. 3G) because transiently bound molecules will yield a nearly constant baseline intensity. We calculated the slow cycle amplitude by extrapolating from two standards with known numbers of GFP-tagged molecules that localized to small spots in yeast nuclei and obtained 42 ± 10 (SD) Ace1-GFP molecules at *CUP1* at the peak of the slow cycle (Fig. 4B). This is much larger than the one or two molecules expected if the slow cycle is generated from the recruitment and release of stably bound molecules.

Thus, slow cycling by recruitment and release of stably bound activators is contradicted by the measured numbers of both transcribing genes and slow-cycling Ace1-GFP molecules. These results, however, are compatible with an alternate model in which the slow cycle reflects the number of accessible binding sites at promoters and each accessible site can be bound by fast-cycling molecules (Fig. 3B). In this model, FRAP curves will always recover to 100% (Fig. 3D). Furthermore if 75 to 100% of the *CUP1* promoters eventually become accessible to fast-cycling molecules, then a large slow cycle amplitude will arise (Fig. 3H). If these fast-cycling molecules can also initiate transcription, then a large fraction of cells will produce transcripts from the marked promoter (Fig. 3F).

For validation, we performed Monte Carlo simulations (*19*) for both the stable binding and accessibility models (Fig. 3, I and J, and fig. S7). The results of these simulations (Fig. 4, A and B) agreed with the predictions described above. The simulations also generated distinctive predictions from the two models for the kinetics of tagged mRNA accumulation, with the accessibility prediction closely matching the experimental data (fig. S8).

To provide more direct support for the accessibility model, we used ChIP analyses to measure histone occupancy at the *CUP1* promoter. We observed oscillations in the amounts of histones H2A and H3 that inversely mirrored the Ace1p slow cycle (Fig. 4C). These observations do not establish whether these changes in histone



Experiment / Model	% of Cells Expressing the Tagged mRNA
Tagged *CUP1* Transcript	71 ± 4
Stable Binding	*0 - 11*
Accessibility	*70 - 100*

Experiment / Model	Amplitude of Slow Cycle (# of mols)
Tagged Ace1p on Arrays	42 ± 10
Stable Binding	*0.0 - 0.5*
Accessibility	*≤ 40*

Fig. 4. Evidence for slow cycling by accessibility. (**A**) After copper induction, MS2-tagged mRNA appeared as one or two bright spots within nuclei, which then increased in brightness over time. Scale bar, 2 μm. Shown in the table are the percent of transcribing cells using the tagged mRNA and the predictions of the two models. For stable binding, the range is derived from a FRAP-immobile fraction of 0 to 4%, whereas for accessibility the range is derived from the estimated number of 30 to 40 Ace1-GFP molecules at the 40 *CUP1* sites [as determined in (B)]. (**B**) Intensities of GFP-tagged puncta containing either 500 molecules (*22*) (GFP-Spc42p) or 256 molecules (*23*) (GFP-Lac) (see fig. S6 for representative images). Extrapolation yields an average intensity of ~125 triple GFP-Ace1p at the *CUP1* promoters. This corresponds to 42 ± 10 (SD) Ace1p molecules as the peak amplitude of the slow cycle. The table compares this estimate to the Monte Carlo predictions for the stable binding model based on a 0 to 4% FRAP-immobile fraction and for the accessibility model where the amplitude is a free parameter with upper bound given by the total number of *CUP1* sites. (**C**) ChIP with two histone antibodies reveals a cycle in histone occupancy at the *CUP1* promoter that inversely mirrors Ace1p occupancy. Error bars indicate SEM. (**D**) Time-lapse analysis of a chromatin remodeling mutant, *rsc2*Δ, shows impaired recruitment of Ace1p to *CUP1* that dramatically reduces the slow cycle amplitude (see fig. S10 for representative images). *t* = 0 corresponds to the time at which each individual array first became visible. Error bars are SEM. wt, wild type.

occupancy are a cause or an effect of slow cycling, but in either case they are consistent with slow cycling by promoter binding site accessibility.

Changes in histone occupancy at *CUP1* could be mediated by an adenosine triphosphate–dependent chromatin remodeler. By using fluorescence resonance energy transfer, we found that the chromatin remodeler Rsc2p interacts in live cells with Ace1p via its transcriptional activation domain (fig. S9). When Rsc2p was deleted, the Ace1p slow cycle was dramatically altered (Fig. 4D). This suggests that Rsc2p acts to mediate promoter accessibility; however, we cannot exclude the possibility that the effect of the Rsc2p deletion might be indirect, because the RSC remodeling complex may regulate hundreds of yeast genes (*20*, *21*).

The work with this natural yeast system provides insight into the function of fast and slow cycling and suggests that these two events can coexist for a single promoter. The slow changes in mRNA synthesis from the *CUP1* promoter appear to reflect slow changes in the accessibility of promoter binding sites rather than the recruitment and release of stably bound Ace1p transcriptional activators. Once accessible, the *CUP1* promoter can then be bound by Ace1p, with these transient interactions giving rise to the fast cycle and the production of transcripts. Hence, our data suggest that at this promoter the fast cycle is responsible for transcriptional initiation and the slow cycle for adjusting the amount of mRNA synthesis.

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Centromeric Aurora-B Activation Requires TD-60, Microtubules, and Substrate Priming Phosphorylation

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The chromosome passenger complex (CPC) controls chromosome congression, kinetochore-microtubule attachments, and spindle checkpoint signaling during mitosis. Aurora-B kinase is the catalytic subunit of the CPC. To understand how a single kinase can regulate such diverse events, we have investigated the activation of Aurora-B and describe two distinct activation mechanisms. First, Aurora-B activation in vitro requires two cofactors, telophase disc–60kD (TD-60) and microtubules. TD-60 is critical to localize both the CPC and Haspin kinase activity to centromeres and thus regulates Aurora-B at several levels. Second, Aurora-B substrates can inhibit kinase activation, and this is relieved by phosphorylation of these substrates by the centromeric kinases Plk1 and Haspin. These regulatory mechanisms suggest models for phosphorylation by Aurora-B of centromeric substrates at unaligned chromosomes and merotelic attachments.

Aurora-B kinase is individually regulated at each centromere where it phosphorylates distinct sets of substrates at each mitotic stage to direct chromosome segregation (*1*). Aurora-B activity requires interaction with its partner INCENP (*2*–*4*) and (auto)phosphorylation of its T-loop (*5*, *6*). Phosphorylation of an Aurora-B site on the C terminus of INCENP (S850) increases activity by a factor of 8 to 10. TD-60, another inner centromere protein, is required for centromeric targeting of the CPC and for chromosome congression (*7*). To understand how TD-60 and Aurora-B interact, we cloned, expressed, purified, and raised antibodies against *Xenopus* TD-60 (fig. S1, A and B) and showed that TD-60 immunoprecipitated from *Xenopus* extracts pulled down CPC subunits Dasra-A and INCENP (Fig. 1A and fig. S1D). Reciprocal immunoprecipitations with INCENP and Dasra-A confirmed the interaction.

To examine TD-60's role in recruiting the CPC during mitosis, we immunodepleted TD-60 from *Xenopus* cytostatic factor (CSF) extracts (fig. S1C), cycled them into S phase, and rearrested in the following metaphase, allowing spindle formation. TD-60–depleted extracts were impaired in their ability to align chromosomes to the metaphase plate (Fig. 1, B to D, and figs. S2A and S3A), as shown in cells (*7*). Phosphorylation of a well-defined chromatin substrate of Aurora-B kinase, serine 10 of histone-H3 (H3S10), was not affected by TD-60 depletion (Fig. 1D and fig. S2B). However, phosphorylation of histone-H3 on threonine-3 (H3T3), a known centromeric target of Haspin kinase (*8*, *9*), required TD-60 (Fig. 1D). Loss of TD-60 also mislocalized Aurora-B and INCENP from the inner centromere (Fig. 1, B and C, and fig. S2B), as seen after small interfering RNA knockdown of TD-60 in cells (*7*). Adding recombinant TD-60 protein to depleted extracts restored congression and CPC localization to the centromere (Fig. 1, B and C, and fig. S2B). Therefore, TD-60 controls Aurora-B localization and the Haspin kinase activity at the centromere, but TD-60 is not required for Aurora-B activity on chromosome arms.

About 10% of endogenous TD-60 was sufficient to localize Aurora-B to centromeres (Fig. 2, A to D). Chromosome congression defects were still seen in 60% of spindles from the partially depleted extracts (Fig. 2, B and C, and fig. S3A). Although approximately 80% of the endogenous amount of centromeric Aurora-B properly localized to the centromere, phosphorylation on its T-loop was reduced by 97% compared with immunoglobulin G (IgG)–depleted extracts (Fig. 2B, D). Similarly, 70% of INCENP localized to centromeres, but staining of centromeres with the α-pS850 antibody was reduced by 98% (Fig. 2, C and D). We conclude that a small amount of TD-60 is sufficient to localize the CPC to the centromere, but a greater amount is required to activate centromeric Aurora-B kinase.

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The activity of immunoprecipitated CPC was not affected by incubation with physiological concentrations (11 nM) of recombinant TD-60 (Fig. 3A and fig. S4A). Aurora-A kinase, an Aurora-B paralog, is stimulated by microtubules (*10*). Combinations of taxol-stabilized microtubules (10 μM) and TD-60 (7.2 μM, 180 pmol) stimulated Aurora-B kinase activity at concentrations where neither microtubules nor TD-60 had an effect (Fig. 3A). Aurora-B and full-length INCENP (fig. S4B, AI) bind microtubules, consistent with the previously identified microtubule-binding activity in the central region of INCENP (*11*, *12*). However, there is at least one additional microtubule-binding site in either Aurora-B (60-361) or a small C-terminal fragment of INCENP (790-856) (fig. S4B, $AI^{790\text{-}856}$). Recombinant TD-60 independently bound microtubules. We conclude that both Aurora-B/INCENP and TD-60 directly interact with microtubules and that all four components are required for kinase activation.

To study Aurora-B activation in a defined system, we developed a three-step in vitro assay using highly purified components (Fig. 3B). Because Aurora-B phosphorylates both its own T-loop and the C terminus on INCENP, it is fully active when expressed with INCENP and purified from *Escherichia coli.* To study Aurora-B activation, we first dephosphorylated recombinant $AI^{790\text{-}856}$ (*13*) by λ-phosphatase. Second, λ-phosphatase was inhibited with sodium orthovanadate (vanadate) and the kinase was incubated with presumptive activators. Third, kinase activity was assayed upon addition of histone H3 as a substrate with γ^{32}P-ATP (adenosine triphosphate) (Fig. 3, B and C). After inactivation by phosphatase treatment, Aurora-B could not activate itself after 30 min (Fig. 3, B to D). Although microtubules on their own partially stimulated the kinase, a time course demonstrated synergistic activation by a combination of TD-60 and microtubules (Fig. 3, C and D). Together the two cofactors stimulated Aurora-B kinase activity by a factor of more than 100 and showed cooperative kinetics with a 2.5-min lag-phase during which the T-loop of Aurora-B was autophosphorylated (Fig. 3, C and D). This cooperativity suggests positive feedback by Aurora-B kinase in trans.

In the previous experiment, Aurora-B/INCENP was incubated with cofactors without nucleotide first, and then the substrate and γ^{32}P-ATP were added last. The order of addition of components affected the reaction. We preincubated three of four components with unlabeled ATP and then added the fourth component and γ^{32}P-ATP to measure kinase activity. Preincubation of microtubules, TD-60, and the CPC with ATP eliminated the lag phase, which suggests that these components are sufficient to activate Aurora-B. All conditions that included the histone-H3 substrate in the preincubation step prevented kinase activation (Fig. 4A). The experiment in Fig. 4A was performed with the CPC complex (fig. S1E), and similar results were seen using $AI^{790\text{-}856}$ (fig. S5A). We saw similar effects when myelin basic protein was the substrate (fig. S5B). These data demonstrate that preincubation of substrates with inactive kinase inhibits subsequent kinase activation by microtubules and TD-60.

If substrates prevent Aurora-B activation, there must be mechanism(s) to reverse this inhibition. We hypothesized that phosphorylation of Aurora-B substrates by other kinases would reverse the inhibitory effect. Peptides of the histone-H3 N terminus were preincubated with TD-60, followed by the addition of the CPC, microtubules, and unlabeled ATP. Activity was measured after addition of γ^{32}P-ATP and myelin basic protein substrate for 2 min. Preincubation with an unphosphorylated histone-H3 peptide potently inhibited kinase activation (K_i-50 nM) (Fig. 4B). However, when this peptide was phosphorylated on T3, the kinase was activated with myelin basic protein (Fig. 4B) or MCAK-S196 (fig. S7A) as a substrate. Thus, H3 tails inhibit kinase activation unless they are phosphorylated on T3. We propose that Haspin phosphorylation of T3 at the centromere facilitates Aurora-B activation.

Unphosphorylated substrates presumably bind either Aurora-B/INCENP (fig. S1F) or TD-60 to inhibit activation. The unphosphorylated H3 peptide bound Aurora-B/INCENP much more strongly than did the phosphorylated peptide (Fig. 4C). TD-60 poorly bound either peptide at the concentrations tested. These data suggest that unphosphorylated substrates directly bind Aurora-B/INCENP to prevent activation.

TD-60 is required for H3S10 phosphorylation in vitro but not in vivo. We tested the requirement for cofactors (TD-60 and microtubules) and priming phosphorylation on a physiological centromeric substrate. The microtubule depolymerase MCAK is phosphorylated by Aurora-B on S196 and T95 in the centromere in prometaphase and on T95 on chromosome arms in prophase (*14*–*17*). Microtubules poorly stimulated total kinase activity on MCAK(2-263), and TD-60 did not further stimulate activity (fig. S5C).

We determined whether a priming phosphorylation could restore TD-60 and microtubule

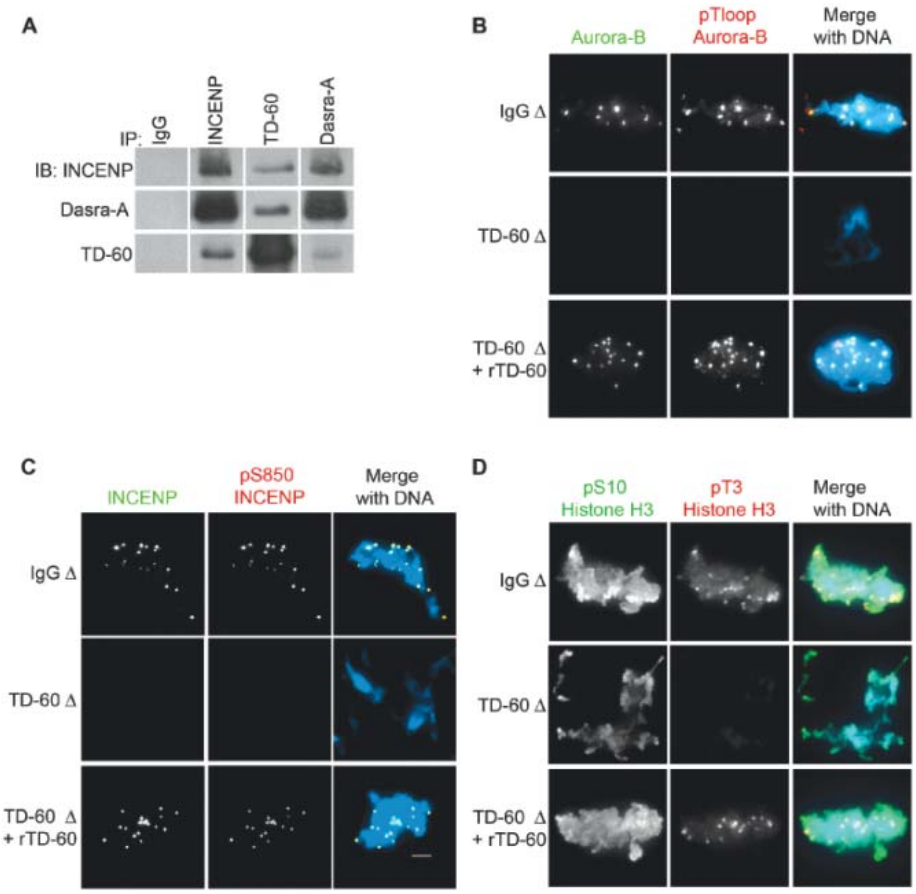

Fig. 1. TD-60 is required to congress chromosomes and localize CPC and Haspin kinase activity to the centromeres. (**A**) CPC and TD-60 interact in Xenopus CSF extracts. (**B** to **D**) Representative spindles from mock-depleted extracts (IgGΔ), TD-60–depleted extracts (TD-60Δ), or TD-60–depleted extracts rescued with recombinant TD-60 (TD-60Δ+rTD-60), stained with the antibodies indicated at the top of each panel. Scale bar, 10 μm.

cooperative activation of Aurora-B on MCAK. Another centromeric kinase, the *Xenopus* Polo kinase (Plx1), phosphorylates MCAK. Plx1 immunoprecipitated from mitotic *Xenopus* extracts phosphorylated MCAK as well as Aurora-B in this assay (fig. S6B). Further analysis of Plx1 phosphorylation on MCAK mapped the majority of Plx1 sites to the N-terminal region (2 to 116) (fig. S6, A and C).

To directly test whether priming phosphorylation by Plx1 activates MCAK as an Aurora-B substrate, we measured the kinetics of Aurora-B kinase activity on two different Aurora-B sites on MCAK(2-263) by immunoblots using antibodies specific to phosphorylated residues T95 and S196 (*14*–*17*). In a control reaction in which MCAK was incubated with Aurora-B, there was little activity on MCAK (Fig. 4D and fig. S7C, MCAK only). Preincubating Plx1 with MCAK before the addition of Aurora-B produced robust phosphorylation on the MCAK-T95 site but little activity on the MCAK-S196 site. MCAK-T95 phosphorylation was seen in all conditions where Plx1 was preincubated with MCAK, which suggests that this is the key event to allow Aurora-B to phosphorylate this site. We believe the stimulation is caused by Plx1 phosphorylation of MCAK on unidentified sites, because Plx1 robustly phosphorylates the N terminus of MCAK (fig. S6, A to C) but does not phosphorylate TD-60 (fig. S6B), MCAK-S196, or MCAK-T95 (fig. S7B).

After phosphorylation with Plx1, MCAK-S196 phosphorylation required the same cofactors as histone-H3. The greatest activation was seen when Plx1 was preincubated with MCAK and then both microtubules and TD-60 were added (Fig. 4D and fig. S7C). Preincubation of MCAK with Plx1 followed by either TD-60 or microtubules alone produced substantial activity, although neither gave as robust activity as when both cofactors were present.

Our data are consistent with the following model of Aurora-B activation (Fig. 4E). Aurora-B requires a rotation to bring the N- and C-terminal domains into register (*13*), which we

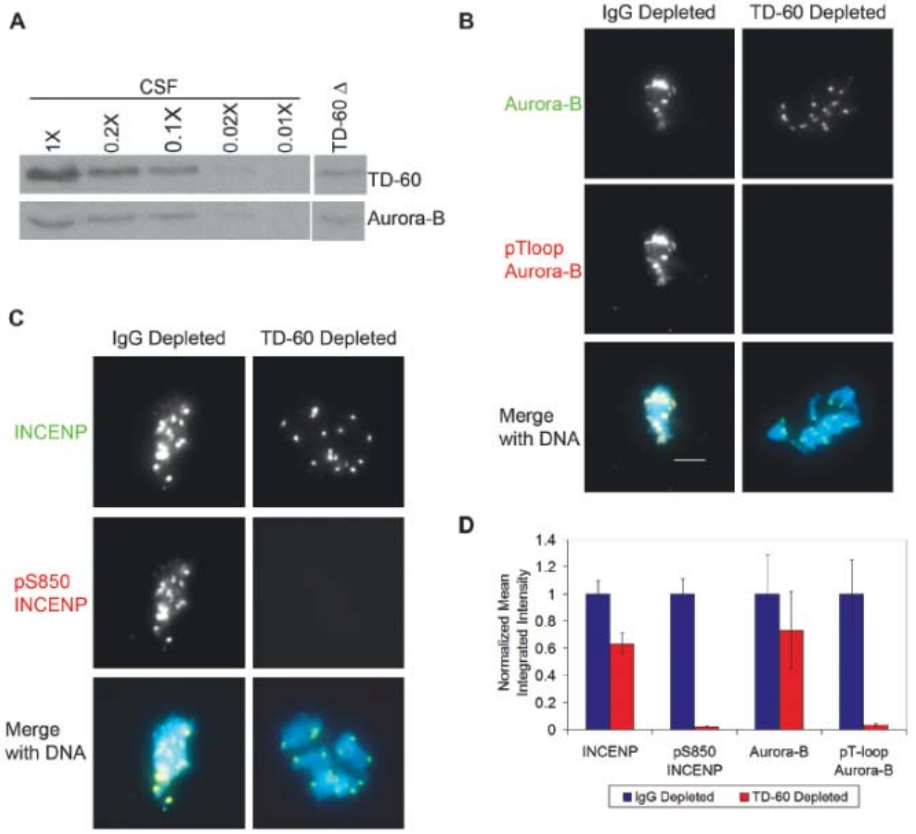

Fig. 2. Partial depletion of TD-60 reveals requirement for TD-60 in Aurora-B activation. (**A**) Immunoblot showing that 10% of endogenous TD-60 remains after depletion. (**B** and **C**) Residual endogenous TD-60 after depletion is sufficient to localize Aurora-B (B) and INCENP (C) to centromeres but not to activate Aurora-B kinase as measured by phosphorylation of the T-loop (B) or INCENP-S850 (C). (**D**) Quantification of mean integrated fluorescence intensity for (B) and (C). *N* = 10 nuclei, 16 centromeres per nuclei. Error bars represent SEM. Scale bar, 10 μm.

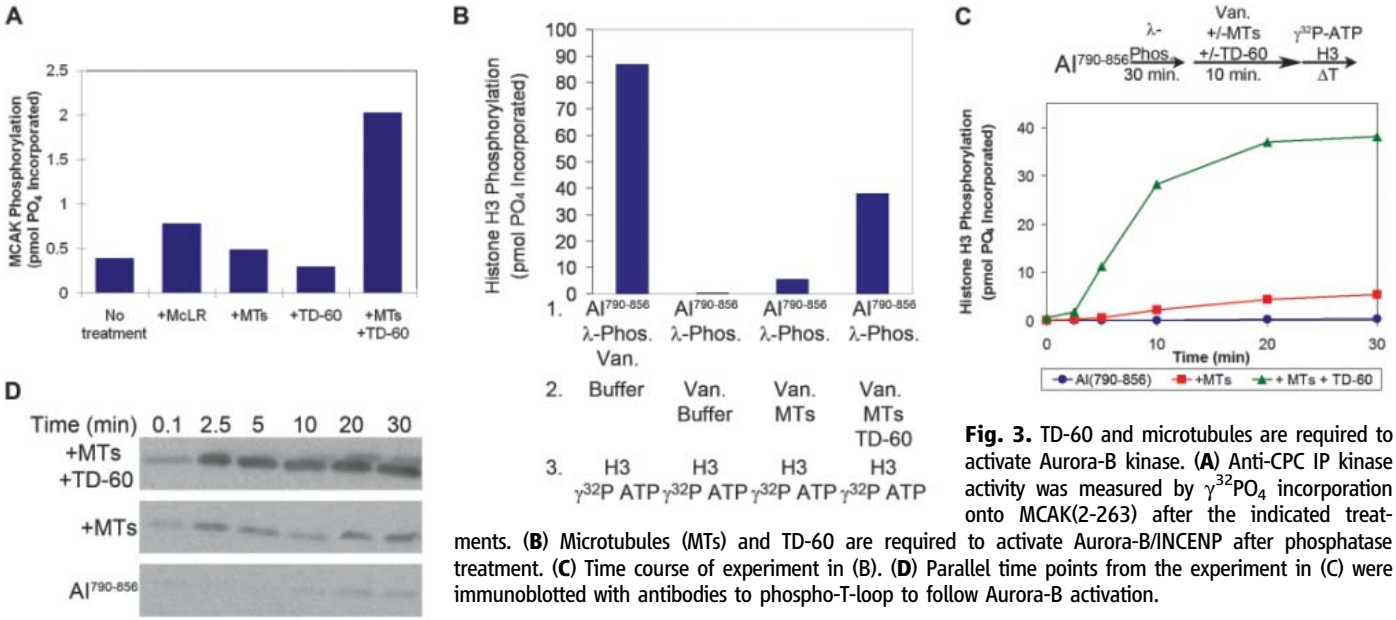

Fig. 3. TD-60 and microtubules are required to activate Aurora-B kinase. (**A**) Anti-CPC IP kinase activity was measured by $\gamma^{32}PO_4$ incorporation onto MCAK(2-263) after the indicated treatments. (**B**) Microtubules (MTs) and TD-60 are required to activate Aurora-B/INCENP after phosphatase treatment. (**C**) Time course of experiment in (B). (**D**) Parallel time points from the experiment in (C) were immunoblotted with antibodies to phospho-T-loop to follow Aurora-B activation.

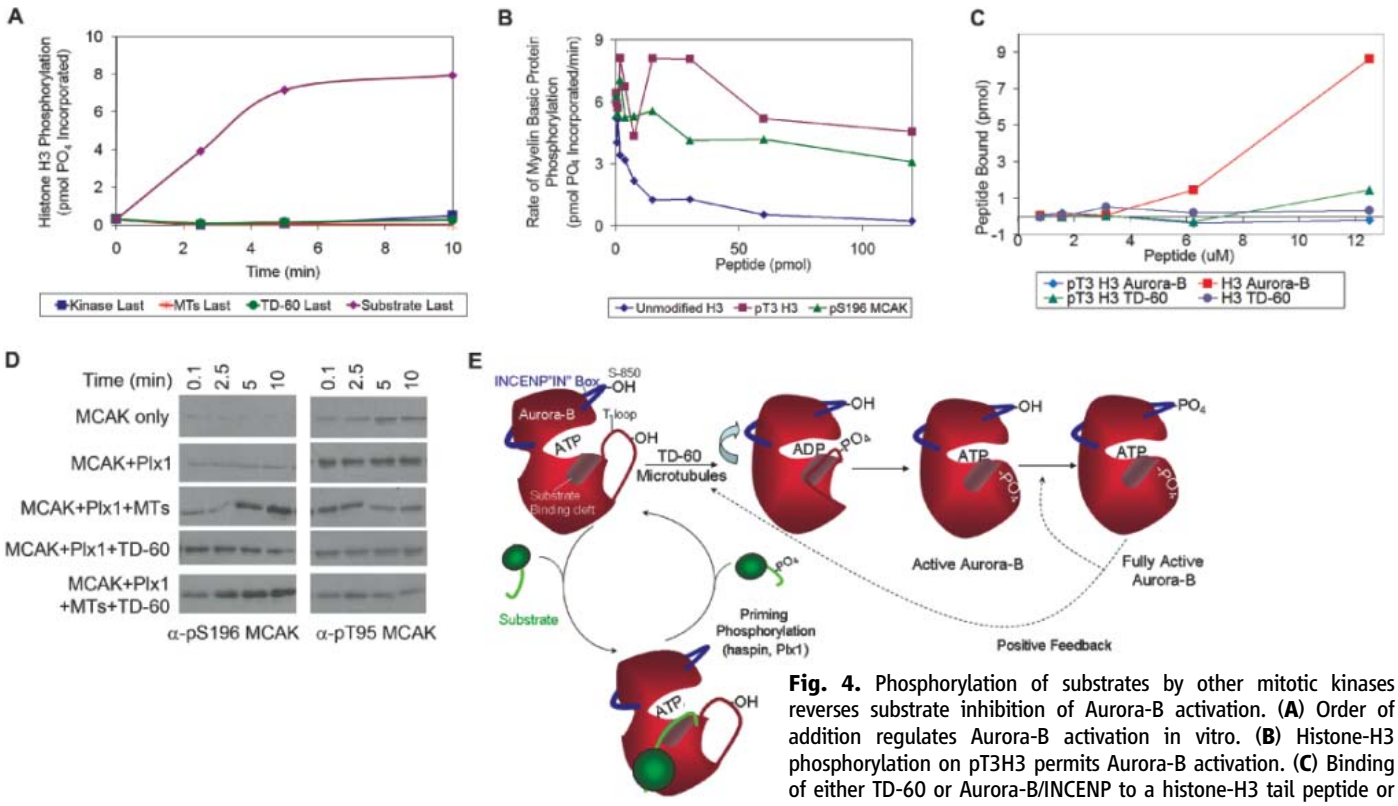

Fig. 4. Phosphorylation of substrates by other mitotic kinases reverses substrate inhibition of Aurora-B activation. (**A**) Order of addition regulates Aurora-B activation in vitro. (**B**) Histone-H3 phosphorylation on pT3H3 permits Aurora-B activation. (**C**) Binding of either TD-60 or Aurora-B/INCENP to a histone-H3 tail peptide or the same peptide phosphorylated on T3. (**D**) Plx1 was incubated with MCAK and ATP, followed by addition of Aurora-B/INCENP and indicated cofactors. Phosphorylation of MCAK by Aurora-B was measured by immunoblot with indicated phosphospecific antibodies. (**E**) Model for Aurora-B activation by TD-60, microtubules, and substrate priming.

propose is the step catalyzed by TD-60 and microtubules to allow T-loop autophosphorylation. Active kinase phosphorylates activation sites on inactive CPCs, generating positive feedback. Substrates inhibit activation because they compete with the T-loop for the active site or block domain rotation. Priming phosphorylation dissociates substrates from Aurora-B, allowing activation.

Our data suggest mechanisms of cross-talk between three major mitotic kinases. CDK1 phosphorylation of substrates recruits Plx1, which then drives local Aurora-B activation by priming substrates. Moreover, Haspin phosphorylation of H3T3 might establish a centromeric histone code that ensures that high Aurora-B activity is restricted to centromeres in prometaphase.

During prophase Aurora-B regulates global events such as changes to mitotic chromatin, whereas in prometaphase each mitotic chromosome is autonomously controlled by Aurora-B activity to generate spindle checkpoint signals and correct kinetochore-microtubule attachments. Currently the best example of these phenomena is the regulation of MCAK by Aurora-B. Can the interplay of substrate inhibition and cofactor availability to control Aurora-B activity explain the spatial and temporal changes seen in MCAK regulation? In G2/Prophase, the CPC may use Plx1 priming phosphorylation to phosphorylate MCAK-T95 throughout the nucleus (*16*, *17*). In anaphase, the CPC, TD-60, and Plx1 are colocalized on midzone microtubules spatially restricting MCAK-S196 phosphorylation to this region (*14*). In prometaphase, phosphorylation of MCAK-S196 is enriched on the centromeres of unaligned chromosomes and also at centromeres of chromosomes that have a kinetochore attached to both poles (merotelic attachments) (*18*). This chromosome autonomous regulation may be explained by the requirement of a physical contact between microtubules and Aurora-B during activation. Centromeres on unaligned chromosomes may have frequent contact with microtubules nucleated by centrosomes, whereas the kinetochores of aligned chromosomes could protect inner centromeres from microtubules nucleated from the poles (fig. S7D). An exception would be a merotelic attachment where microtubules are brought into contact with inner centromeres even on chromosomes at the metaphase plate (*18*–*20*). In this way, Aurora-B provides information to centromeres on the location of each chromosome on the spindle as well as its microtubule attachment status.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/319/5862/469/DC1
Materials and Methods
Figs. S1 to S7
References

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Alignment Uncertainty and Genomic Analysis

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The statistical methods applied to the analysis of genomic data do not account for uncertainty in the sequence alignment. Indeed, the alignment is treated as an observation, and all of the subsequent inferences depend on the alignment being correct. This may not have been too problematic for many phylogenetic studies, in which the gene is carefully chosen for, among other things, ease of alignment. However, in a comparative genomics study, the same statistical methods are applied repeatedly on thousands of genes, many of which will be difficult to align. Using genomic data from seven yeast species, we show that uncertainty in the alignment can lead to several problems, including different alignment methods resulting in different conclusions.

A common theme in comparative genomics studies is a flow diagram, or chart, tracing the various steps and algorithms used during the analysis of a large number of genes. Flow charts can be quite sophisticated, with steps such as identifying orthologous gene sets, aligning the genes, and performing different statistical analyses on the resulting alignments. The key point, and a great practical difficulty in comparative genomics studies, is that the analyses must be repeated many times. The procedure, then, is largely automated, with scripting languages such as Perl or Python cobbling together individual programs that perform each step. In addition, many of the individual steps involve procedures originally developed in the evolutionary biology literature, to perform phylogeny estimation or to identify individual amino acid residues under the influence of positive selection (*1*). Statistical methods that until recently would have been applied to a single alignment, carefully constructed, are now applied to a large number of alignments, many of which may be of uncertain quality and cause the underlying assumptions of the methods to fail.

How might alignment uncertainty affect genomic studies? We performed a study designed to uncover the effect that alignment has on inferences of evolutionary parameters. We examined genomic data from seven yeast species (*Saccharomyces cerevisiae*, *S. paradoxus*, *S. mikatae*, *S. kudriavzevii*, *S. bayanus*, *S. castellii*, and *S. kluyveri*). Earlier molecular evolution studies that included these species established the appropriateness of sequence comparisons between them (*2*–*4*), with estimated divergence dates from *S. cerevisiae* ranging from as little as 5 million years for *S. paradoxus* to about 100 million years for *S. kluyveri* and average pairwise sequence similarity ranging from 54 to 89%. The comparisons we carried out among the seven yeast species are, thus, reasonable and of the sort that any evolutionary biologist might make. Accurate inference of evolutionary processes from molecular sequences also relies on the compared sequences being orthologous. However, correct identification of orthologous sequences is not trivial because current alignment algorithms do not evaluate homology and will align sequences regardless of proper evolutionary relationships. We combined two earlier data sets of previously identified orthologous open reading frames (ORFs) from studies on the comparative genomics analysis of yeast (*3*, *4*). The orthologs identified from the Kellis *et al*. (*4*) study were used for species that overlapped between the two studies (*S. mikatae* and *S. bayanus*), and only those ORFs for which all seven species contained a detected orthologous sequence were included in the analysis. Overall, we considered a total of 1502 sets of orthologous gene sequences.

For each orthologous gene set, we applied seven different alignment programs—Clustal W, Muscle, T-Coffee, Dialign 2, Mafft, Dca, and ProbCons (*5*–*11*)—aligning data by amino acid sequence under default program settings and using the aligned amino acid sequences to construct nucleotide alignments. From this intensive undertaking, we produced a table of 1502 × 7 alignments. Alignments were then subjected to several statistical analyses of the sort that an evolutionary biologist might apply; specifically, we estimated the phylogeny using maximum likelihood under the GTR+Γ model of DNA substitution and the number of positively selected sites for each alignment (*1*).

Estimates of phylogeny and inferences of positive selection were sensitive to alignment treatment. Confirming previous studies showing that alignment method has a considerable effect on tree topology (*12*–*14*), we found that 46.2% of the 1502 ORFs had one or more differing trees depending on the alignment procedure used. The number of unique trees outputted for each ORF varied from one to six, and the average symmetric-difference distance (*15*) between trees for each ORF ranged from 0 to 6.67 (for trees of seven species, the maximum possible value is eight). Figure 1 shows a case in which alignments produced by the seven different alignment programs resulted in six different estimates of phylogeny. In general, phylogenies estimated from different alignments for an ORF were more concordant when the alignments were similar. Figure 2A shows a strong positive relation between a measure of variability in alignments across alignment treatments and the average topological distance between estimated trees (*15*). The support for the maximum-likelihood trees, measured by the nonparametric bootstrap, was generally lower when alignments were dissimilar across treatments (Fig. 2B). One does not usually find strongly supported, but conflicting, phylogenies produced by different alignment treatments.

Previous studies on the effects produced by different alignment methods focused on tree topology. Yet, other commonly estimated evolutionary parameters, such as substitution rates and the frequency of positively selected sites, are also alignment dependent. To examine if variable alignments for an ORF affect the inference of these parameters, we estimated the synonymous (d_S) and nonsynonymous (d_N) substitution rates for each gene and inferred sites under positive selection using Paml, under the M2 model with (initially) a threshold of 0.5 for inferring a site to be under positive selection (*1*). Overall estimates of substitution rates did not differ significantly among alignment treatments (Kruskal-Wallis test: d_N, $P = 0.59$; d_S, $P = 0.08$; d_N/d_S, $P = 0.51$), and for most ORFs none of the sites were inferred as under positive selection, regardless of the alignment treatment (1032 ORFs). However, of the remaining 470 ORFs, only 44 showed a consistent number of positively selected sites. Thus, in 28.4% of the cases, we found that the inference of positively selected sites was also sensitive to the method of alignment. Raising the threshold for flagging sites as under the influence of positive natural selection to 0.95 reduced the number of conflicting ORFs (Fig. 3); in 14.8% of the cases, positive-selection inference was sensitive to alignment treatment. However, reducing conflict among alignment treatments comes at the cost of finding fewer sites under positive selection, and in many cases alignment treatments still produce discordant inferences of positive selection.

We hypothesize that the inconsistent inferences of alignments produced by the seven different alignment methods examined here is not necessarily a fault of the alignment procedures, but rather reflects underlying variability in the processes of substitution, insertion, and deletion that makes some ORFs inherently more difficult to align. We examined alignment variability by approximating the marginal posterior probability distribution of the alignment for each ORF, using the program BAli-Phy (*16*, *17*). BAli-Phy implements a stochastic model of insertion and deletion and explores posterior probability distributions of phylogenetic model parameters, such as the tree and branch lengths, as well as the

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probability distribution of alignment by Markov chain Monte Carlo (MCMC). Quantifying the uncertainty of complex discrete random variables, such as alignments, is a formidable task. We developed a crude summary statistic that reflects variability of the alignments sampled with MCMC for each ORF; we calculated a distance between all pairs of sampled alignments and considered the mean of these pairwise distances as a measure of inherent alignment uncertainty for each ORF. To measure distances between alignments, we exploited the metric of Schwartz *et al*. (*18*). Effectively, this metric counts the number of pairwise homology statements upon which two alignments disagree. We found that alignment variability, as reflected by the marginal posterior probability distribution of alignments, was associated with the inconsistency of alignments produced by the seven different alignment methods (Fig. 2C) and with the number of estimated nonsynonymous substitutions for an ORF (Fig. 2D).

The problem of alignment uncertainty in genomic studies, identified here, is not a problem of sloppy analysis. Many comparative genomics studies are carefully performed and reasonable in design. However, even carefully designed and carried out analyses can suffer from these types of problems because the methods used in the analysis of the genomic data do not properly accommodate alignment uncertainty in the first place. Moreover, the genes that are of greatest interest to the evolutionary biologist probably suffer disproportionately. For example, in several studies, the genes of greatest interest were the ones that had diverged most in their nonsynonymous rate of substitution (*19*). But, these are the very genes that should be the most difficult to align in the first place. We also do not believe that the alignment uncertainty problem is one that can be resolved by simply throwing away genes, or portions of genes, for which alignment differs. Quality checks are common in comparative genomics studies, often referred to as "filters" in a flow diagram showing the analyses that were performed. The filters usually exclude

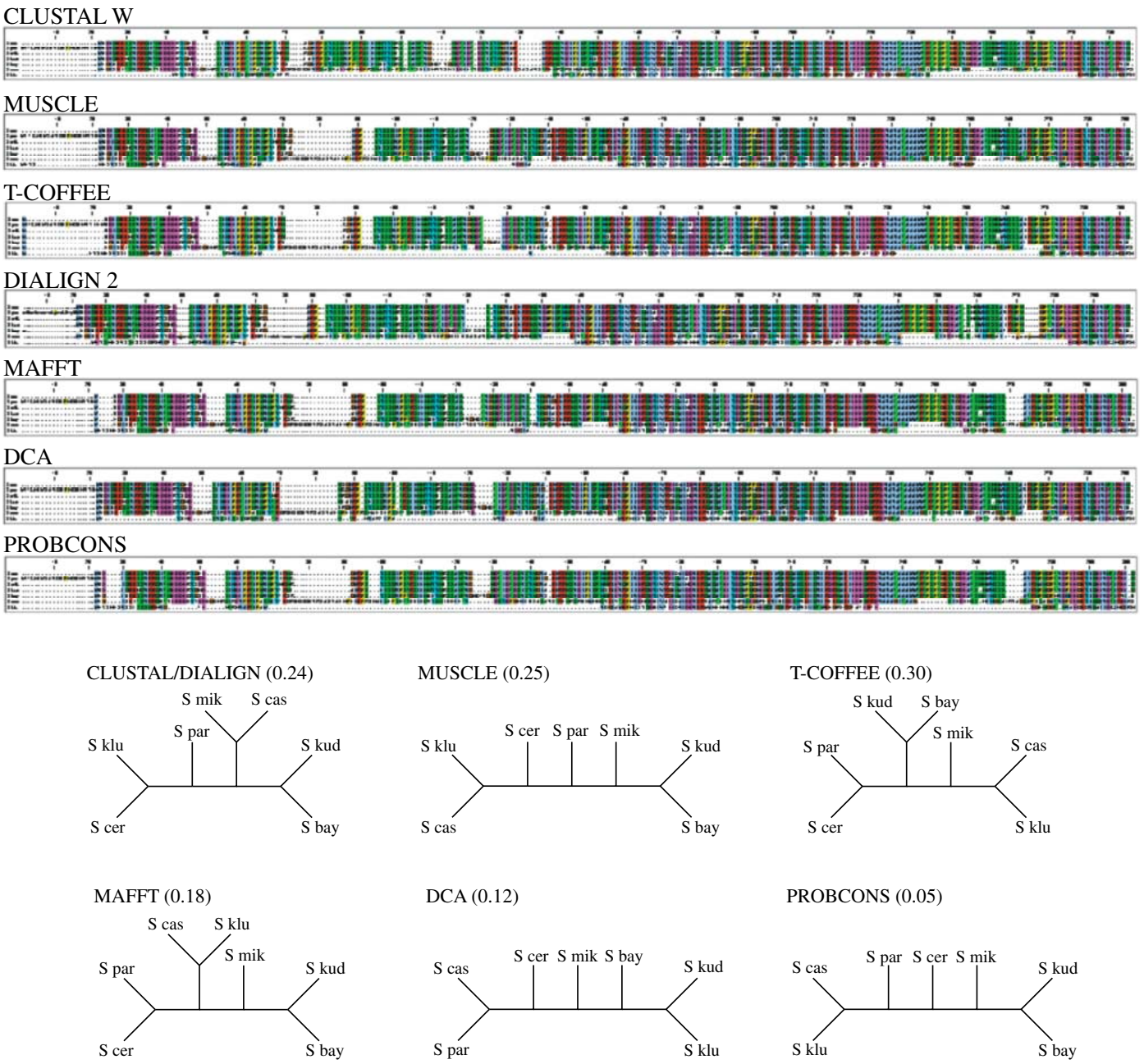

Fig. 1. An example, involving ORF YPL077C, in which alignments produced by seven different alignment methods produce six different estimated trees, albeit with low bootstrap support (bootstrap proportions shown parenthetically for each tree).

ambiguous alignment regions according to some criterion. Discarding information from alignments is inadvisable for at least two reasons. First, one may end up discarding considerable portions of the primary data, some of which may be informative. In some cases, insertion and deletion events themselves are informative for phylogeny estimation (*20*). In other cases, excluding a gapped position leads to excluding substitutions that occur elsewhere in the tree at that site and are informative (*21*). Moreover, excluding data does not necessarily result in more concordant inferences. Figure 2E shows results of phylogenetic analyses in which gapped sites were excluded from the alignments. One still finds many genes for which phylogenetic inferences differ among alignment treatments. Second, when an appropriate statistical method of analysis is applied, one may be able to make conclusions even in the face of alignment uncertainty. For example, it might be that the number and identity of positively selected sites differ among alignment treatments. However, when the alignment uncertainty is properly accounted for, one may still be able to pick out some sites that are consistently under positive selection.

The common statistical procedure for accounting for parameter uncertainty is to treat the parameter as a random variable and sum or integrate over the uncertainty, weighting each possible value of the parameter by its prior probability. In a comparative genomics study, we advocate that alignment be treated as a random variable, and inferences of parameters of interest to the genomicist, such as the amount of nonsynonymous divergence or the phylogeny, consider the different possible alignments in proportion to their probability. Considering alignment as a random variable is innate to the statistical alignment pro-

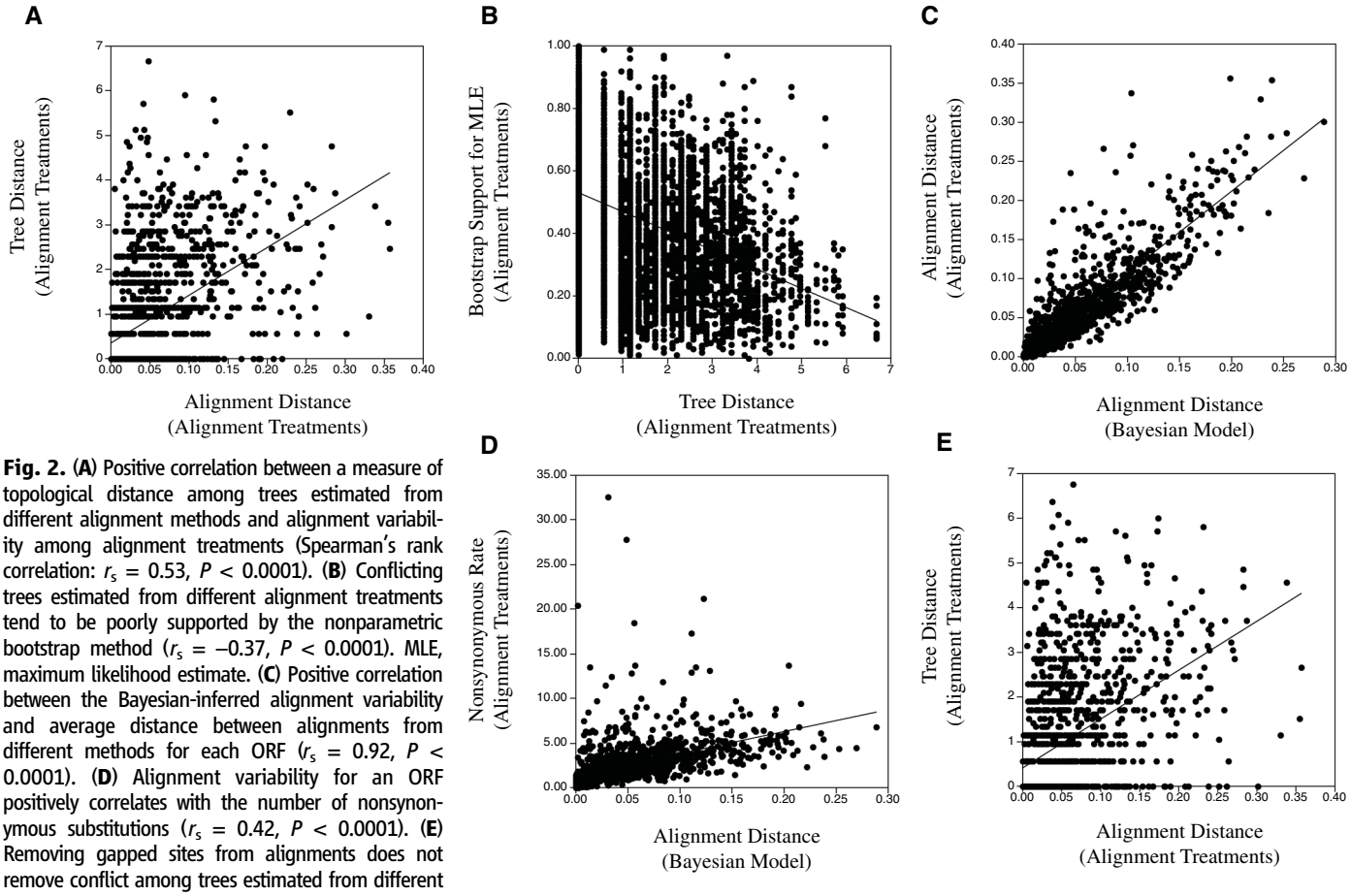

Fig. 2. (**A**) Positive correlation between a measure of topological distance among trees estimated from different alignment methods and alignment variability among alignment treatments (Spearman's rank correlation: $r_s = 0.53$, $P < 0.0001$). (**B**) Conflicting trees estimated from different alignment treatments tend to be poorly supported by the nonparametric bootstrap method ($r_s = -0.37$, $P < 0.0001$). MLE, maximum likelihood estimate. (**C**) Positive correlation between the Bayesian-inferred alignment variability and average distance between alignments from different methods for each ORF ($r_s = 0.92$, $P < 0.0001$). (**D**) Alignment variability for an ORF positively correlates with the number of nonsynonymous substitutions ($r_s = 0.42$, $P < 0.0001$). (**E**) Removing gapped sites from alignments does not remove conflict among trees estimated from different alignment treatments ($r_s = 0.52$, $P < 0.0001$).

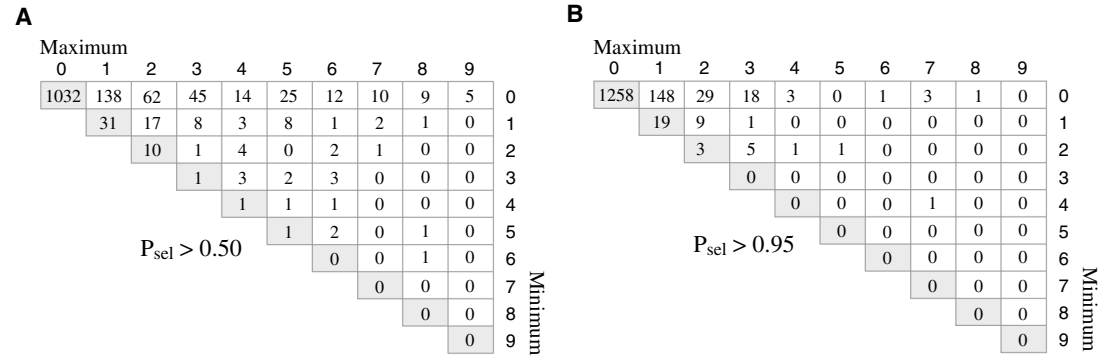

Fig. 3. (**A**) The range in the number of positively selected sites for each ORF. Inferences of positive selection for an ORF are consistent across alignment treatments when the minimum and maximum number of positively selected sites are equal. In many cases (426 of 1502 ORFs), inferences of positive selection varied depending upon the alignment treatment. (**B**) Increasing stringency for inferring positive selection to 0.95 decreases the number of sites inferred to be under positive selection; there remain many cases (222 of 1502 ORFs) in which inferences of positive selection differ according to alignment treatment.

cedure advocated by many (*22*–*24*). Statistical alignment, however, generally assumes that the phylogeny is known, a condition often violated in comparative genomics studies. Moreover, many biologists appear to take the position that when an alignment has been carefully constructed, incorporating uncertainty is unnecessary; in a phylogenetic study, for example, the phylogenetic marker is carefully selected because it is easy to align and has a substitution rate appropriate to the phylogenetic problem of interest (*25*), a selectivity that may help, but probably does not solve, the alignment uncertainty problem in many phylogenetic studies, especially those for anciently diverged species. In comparative genomics studies, however, the goal is to analyze all of the genes in the genome. As we have shown here, many of these genes will be difficult to align and result in highly variable evolutionary parameter estimates. Allowing for uncertainty in the alignment and, possibly, phylogeny simultaneously, through statistical phylo-alignment, should be of special importance in comparative genomics studies.

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NFAT Binding and Regulation of T Cell Activation by the Cytoplasmic Scaffolding Homer Proteins

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T cell receptor (TCR) and costimulatory receptor (CD28) signals cooperate in activating T cells, although understanding of how these pathways are themselves regulated is incomplete. We found that Homer2 and Homer3, members of the Homer family of cytoplasmic scaffolding proteins, are negative regulators of T cell activation. This is achieved through binding of nuclear factor of activated T cells (NFAT) and by competing with calcineurin. Homer-NFAT binding was also antagonized by active serine-threonine kinase AKT, thereby enhancing TCR signaling via calcineurin-dependent dephosphorylation of NFAT. This corresponded with changes in cytokine expression and an increase in effector-memory T cell populations in Homer-deficient mice, which also developed autoimmune-like pathology. These results demonstrate a further means by which costimulatory signals are regulated to control self-reactivity.

T cells are activated through the TCR and costimulatory pathways predominantly mediated by the cell surface receptor CD28. Although these pathways are relatively well defined, questions still remain about how costimulatory signals are regulated. The Homer family of cytoplasmic scaffolding proteins are known to function at the neuronal excitatory synapse (*1*, *2*), although their wide tissue distribution, including within the immune system, suggests that their functions may be relatively broad.

To investigate the in vivo functions of the Homer proteins, we generated mice in which the loci for each Homer gene were deleted (Homer1, 2, and 3). Of these, we noted that the Homer3-deficient mice (*3*) displayed lymphocyte infiltration of multiple organs and hyperplasia in lymph nodes by 10 weeks of age (fig. S1), which suggested that at least one of the family might possess some level of immune function. Because Homer proteins typically have redundant roles (*1*, *2*), we first assessed their possible role in T cell activation, by assaying interleukin-2 (IL-2) production in T cells lacking all three genes (TKO). IL-2 production was increased by a factor of 2 to 6 in anti-CD3–stimulated T cells from Homer TKO mice relative to wild-type controls (Fig. 1A). By contrast, when T cells were activated by costimulation of both CD3 and CD28, no measurable difference in IL-2 production was detected between wild-type and Homer-deficient mice (fig. S2).

To examine the potential role of Homer proteins in T cell activation in more detail, we used short hairpin RNAs (shRNAs) to knock down Homer gene expression in human Jurkat T cells (Fig. 1B). Knockdown of Homer2 or Homer3, but not Homer1, enhanced the expression of a luciferase reporter driven by the IL-2 promoter by a factor of 3 to 6 (Fig. 1C). Homer2 and Homer3 appeared to have redundant functions in these assays because overexpression of Homer2, but not Homer1, could rescue the loss of Homer3 (Fig. 1D). The IL-2 promoter integrates signals from the calcineurin-NFAT, MAPK-AP1, and NF-κB pathways (*4*, *5*); to identify which pathways might be regulated by Homer, we used luciferase reporter constructs under the control of multimerized binding elements for individual transcription factors. The calcineurin-NFAT pathway was preferentially enhanced in cells depleted of Homer2 or Homer3 (Fig. 1E). To respond to calcium signals, NFAT is first dephosphorylated by calcineurin (*4*), and in Jurkat T cells that expressed shRNAs targeting Homer3, enhanced dephosphorylation of the NFATc2 isoform was observed after activation but not under basal conditions (Fig. 1F). No difference

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was detected in key signaling events for other pathways such as Fos and Jun induction for the AP1 pathway or IκB degradation for the NF-κB pathways (Fig. 1F); these results supported the notion that Homer2 and Homer3 function to selectively inhibit calcineurin-NFAT activation.

The upstream events of NFAT dephosphorylation include calcium mobilization and activation of calcineurin. In a comparison of the calcium dynamics in response to CD3 activation in wild-type and Homer TKO primary T cells, no difference was detected (fig. S3A). An analysis of calcineurin activity in Homer3-depleted Jurkat T cells showed normal calcium-

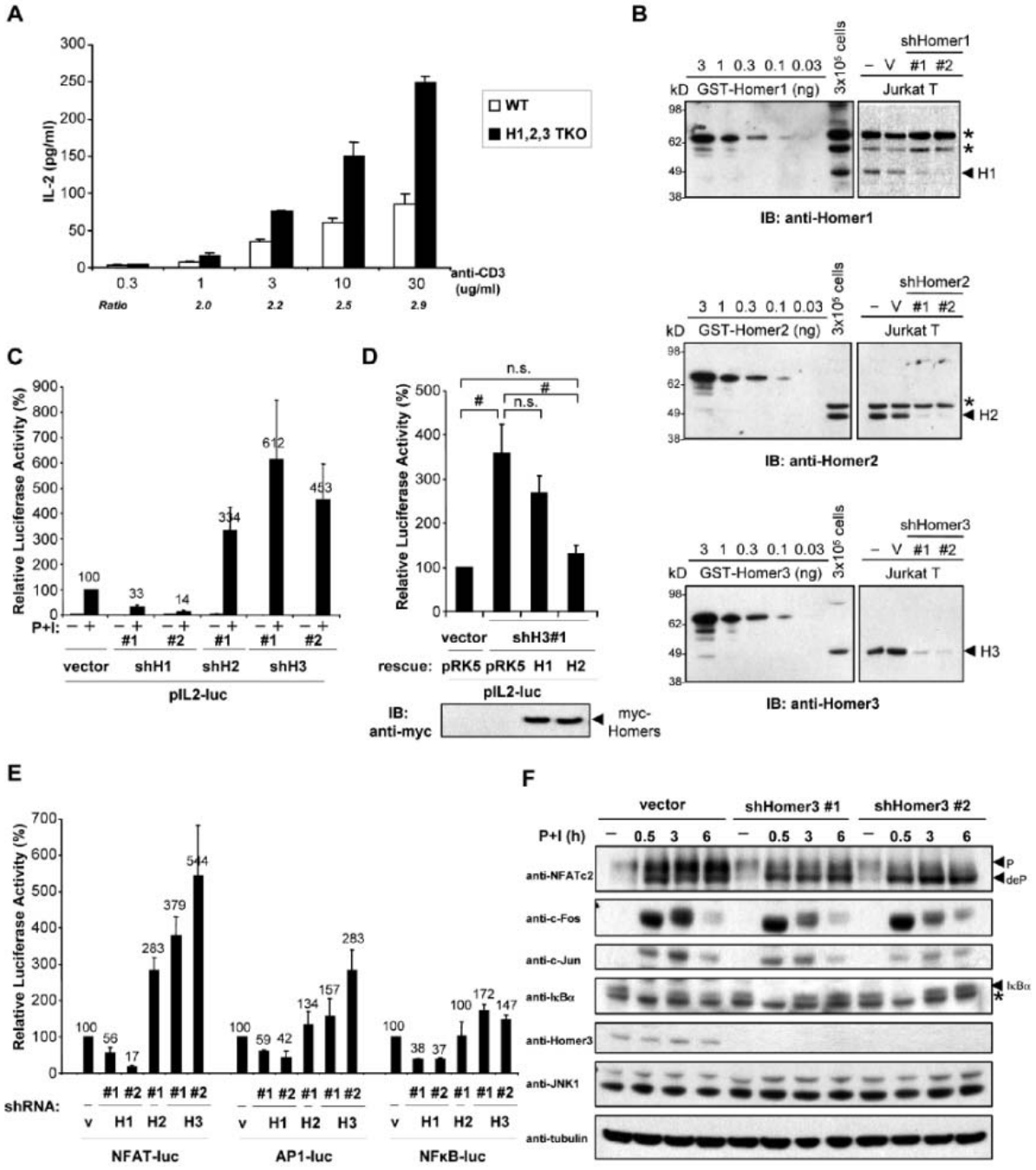

Fig. 1. Homer2 and Homer3 negatively regulate IL-2 expression by inhibiting calcineurin-NFAT pathway activation. (**A**) IL-2 production is enhanced from purified primary Homer1,2,3 triple-knockout (H1,2,3 TKO) T cells after stimulation with anti-CD3 for 24 hours. This result is representative of at least three independent experiments with IL-2 production increases by factors of 4 to 6 from knockout T cells. (**B**) All three Homer family members express in human Jurkat T cells and can be efficiently knocked down by shRNA. (**C**) Depletion of Homer2 or Homer3 enhances IL-2 promoter activity. Jurkat cells were transfected with a luciferase reporter under the control of the IL-2 promoter and Homer shRNA-expressing plasmids and stimulated with PMA (50 ng/ml) and 1 μM ionomycin (P+I). Error bars are SDs from three to seven independent experiments. (**D**) Homer2 and Homer3 have redundant functions in IL-2 expression regulation. Error bars are SDs from three independent experiments; # denotes $P < 0.05$, and n.s. indicates $P > 0.05$ (Student t test). (**E**) Knockdown of Homer2 or Homer3 mainly increases calcineurin-NFAT pathway activation. Cells were stimulated with P+I. Error bars are SDs from three to eight independent experiments. (**F**) Depletion of Homer3 enhances NFAT dephosphorylation. This result is representative of at least three independent experiments. The asterisks in (B) and (F) label the nonspecific cross-reactive proteins.

dependent phosphatase activity (fig. S3B). These results suggested that the Homer proteins function downstream of calcineurin activation but upstream of NFAT dephosphorylation.

We next asked how Homer might inhibit NFAT activation. Coexpression of a green fluorescent protein (GFP)–labeled form of NFATc2 (GFP-NFATc2) with Homer2 or Homer3, but not Homer1, resulted in large cytoplasmic punctae containing both NFATc2 and Homer (Fig. 2A and fig. S4), suggesting physical interaction of the proteins. In support of the notion that Homer directly binds NFAT, purified GST-Homer2 and GST-Homer3 fusion proteins could pull down NFATc1, c2, and c4 isoforms expressed in human embryonic kidney (HEK) cells (Fig. 2B). Homer1 bound only NFATc4, whereas NFATc3 did not show binding to any

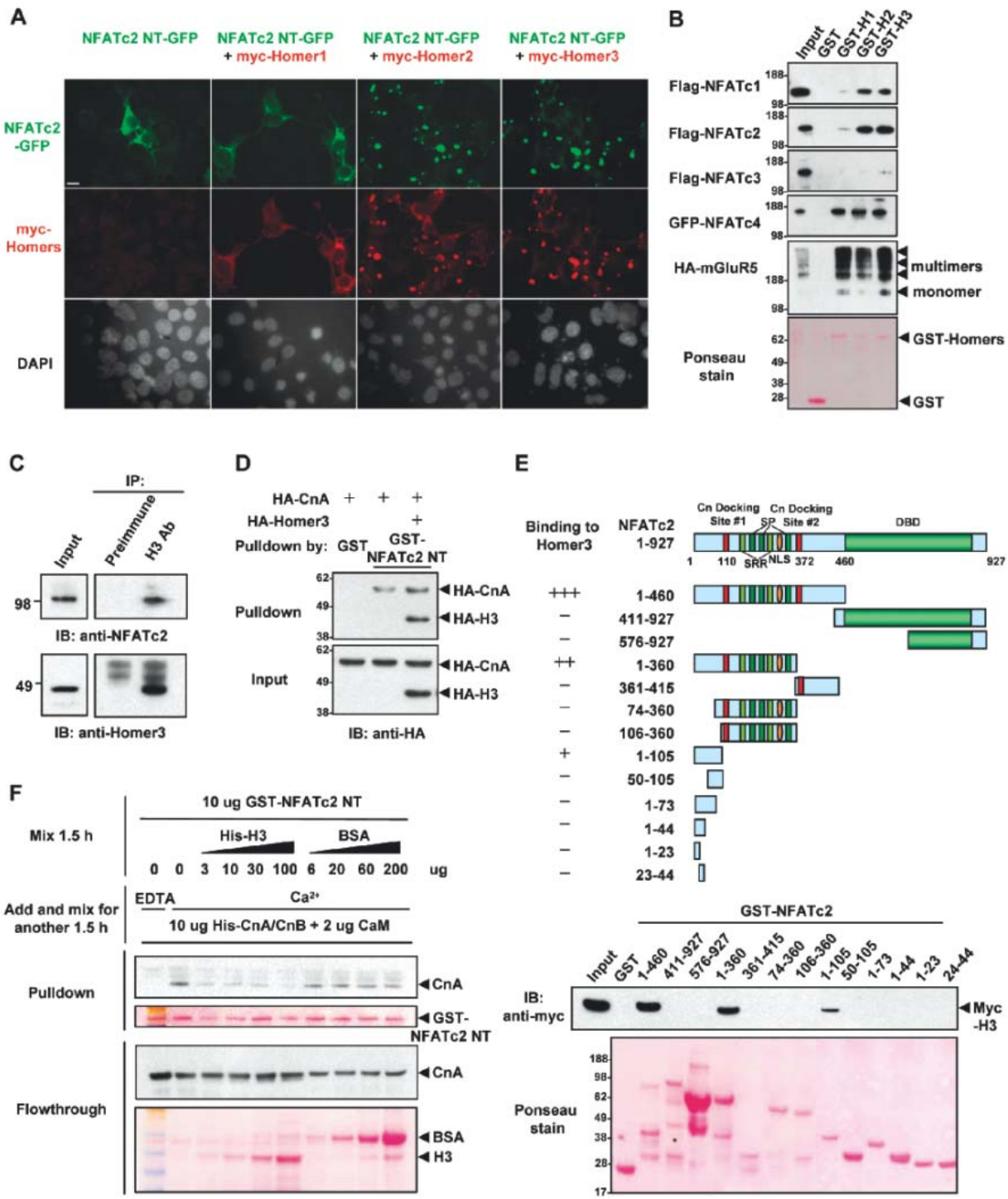

Fig. 2. Homer2 and Homer3 bind NFATc2 and compete with calcineurin for NFATc2 binding. (**A**) NFATc2 forms cytoplasmic punctae in HEK293 cells in the presence of Homer2 or Homer3 overexpression. NFATc2 (1-460) (designated as NT)–GFP is shown in green; Homer proteins are stained in red by an anti-myc mouse antibody. (**B**) Binding specificity between Homer and NFAT family members. mGluR5 binds equally well to Homer1, 2, and 3. (**C**) Coimmunoprecipitation of endogenous Homer3 and NFATc2 from primary mouse T cells. (**D**) GST-NFATc2 NT pulls down comparable amounts of Homer3 and calcineurin. Calcium-containing buffers were used for pull-down assays, and both Homer3 and calcineurin were detected by an antibody to HA. (**E**) Mapping of regions in NFATc2 that bind Homer3. (**F**) Competition between Homer3 and calcineurin for NFATc2 binding.

of the Homer proteins (Fig. 2B). In addition, Homer3 and NFATc2 could be coimmunoprecipitated from whole T cell lysates (Fig. 2C).

We next compared Homer and calcineurin binding to NFATc2. When coexpressed, similar amounts of Homer3 and calcineurin bound GST-NFATc2 (Fig. 2D), which suggested that they have comparable affinities. GST-Homer3 bound NFAT robustly even in calcium-depleted buf-

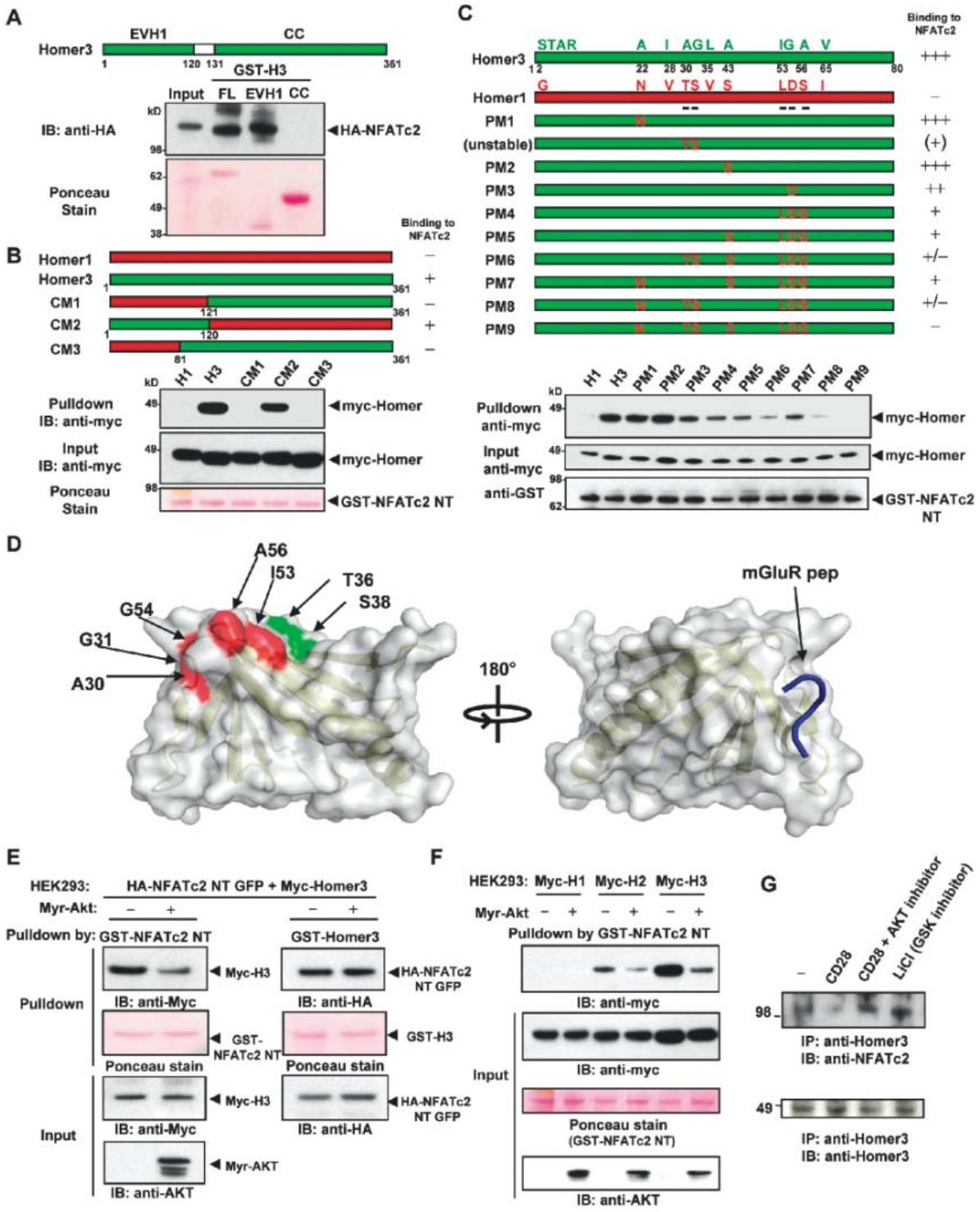

Fig. 3. Five amino acids in the Homer EVH domain distinguish Homer3 from Homer1 for NFATc2 binding. (**A**) The Homer3 EVH domain is sufficient and necessary to bind NFATc2. (**B**) Analysis of Homer3 Homer1 chimeric mutants (CM) reveals that the N-terminal 80 amino acids are critical for NFATc2 binding. (**C**) Analysis of point mutants (PM) of Homer3 with amino acids converted to those in Homer1 for NFATc2 binding. The numbers below the schematic protein bars in (B) and (C) correspond to the positions of the amino acids in Homer3. The five amino acids that are essential for NFATc2 binding are marked by short black bars. (**D**) Crystal structure of the Homer3 EVH1 domain. The five critical amino acids for NFAT binding are labeled in red, and the surface that binds the proline-rich sequence such as mGluR peptide (pep, in blue) is shown. (**E**) Overexpression of active AKT attenuates Homer3-NFATc2 binding. (**F**) Effect of active AKT on NFATc2 binding to Homer family members. (**G**) Activation of CD28 signaling reduces Homer3-NFATc2 binding in primary mouse T cells. T cells were stimulated for 3 hours by anti-CD28 precoated on dishes at 10 μg/ml. An AKT inhibitor (20 μM) or a GSK inhibitor (10 mM LiCl) was added in the medium as indicated.

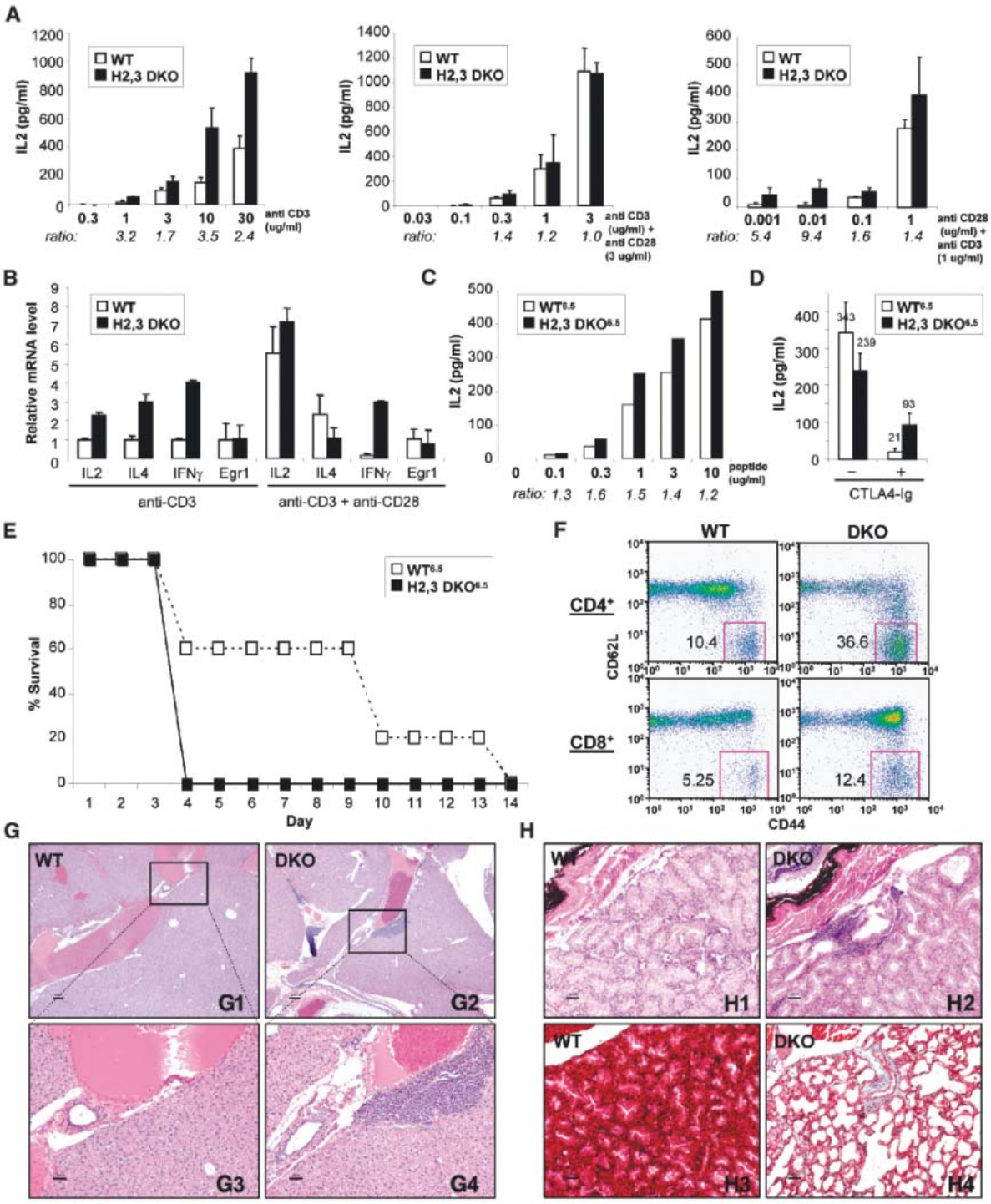

Fig. 4. Deletion of Homer2,3 is linked to autoimmune phenotypes. (**A** and **B**) The costimulatory pathway activation attenuates the difference of IL-2 production between wild type (WT) and Homer2,3 DKO T cells. (A) IL-2 production from purified spleen T cells from wild-type and DKO mice upon stimulation with various dosages of anti-CD3 or anti-CD3 plus anti-CD28. (B) Real-time polymerase chain reaction analysis of gene expression of purified primary T cells stimulated by anti-CD3 (10 μg/ml) or anti-CD3 (3 μg/ml) plus anti-CD28 (3 μg/ml) for 24 hours. (**C** and **D**) IL-2 production from purified $CD4^+$ T cells from wild-type transgenic ($WT^{6.5}$) and Homer2,3 DKO transgenic mice (Homer2,3 $DKO^{6.5}$) 48 hours after mixing with irradiated wild-type APCs in the presence of different concentrations of HA peptide (C) or HA peptide (10 μg/ml) plus CTLA4-Ig protein (5 μg/ml), which blocks the CD28 signaling (D). (**E**) Homer2,3 $DKO^{6.5}$ T cells promote an accelerated response in a pneumonitis autoimmune model. The data of all mice that did not survive are presented. $P = 0.037$ in a log-rank one-way test ($WT^{6.5}$, $n = 5$; Homer2,3 $DKO^{6.5}$, $n = 4$). (**F**) Flow cytometry data showing the staining of the effector-memory T cells ($CD62L^-CD44^{high}$) from 7- to 10-week-old wild-type or DKO splenocytes. The data are representative of three independent experiments in which a total of six animals of each genotype were analyzed. (**G** and **H**) Hematoxylin and eosin stain of the liver (G) and lacrimal gland (H1, H2) sections from 14-month-old wild-type and Homer2,3 mutant mice; trichrome stain of the lacrimal gland sections from a wild-type (H3) and a mutant mouse exhibiting atrophic appearance (H4). Collagen deposition is labeled in blue. Scale bars, 200 μm in (G1) and (G2); 50 μm in (G3), (G4), and (H1) to (H4).

fers (fig. S5A) and was not dependent on NFAT phosphorylation (fig. S5B). NFATc2 contains a DNA binding domain (DBD) and an N-terminal regulatory domain that includes two calcineurin docking sites, serine-arginine–rich regions (SRR), serine-proline–rich regions (SP), and a nuclear localization sequence (NLS) (Fig. 2E) (*6*). Binding assays indicated that Homer3 binds a broad region in the N-terminal regulatory domain (Fig. 2E). Because the Homer binding region overlaps with the calcineurin docking sites on NFAT, we examined whether any of the Homer proteins might compete with calcineurin for NFATc2 binding. Using purified recombinant proteins, we found that Homer3 reduces calcineurin binding to NFATc2 (Fig. 2F).

For all previously described Homer interactions, Homer1, 2, and 3 proteins show identical properties (*1*, *2*). Accordingly, we examined the structural basis of Homer binding to NFATc2 that distinguishes Homer2/3 from Homer1. Binding required the EVH1 domain of Homer3 (Fig. 3, A and B), and mutation analysis identified five amino acids that are most critical (Fig. 3C). The crystal structure of Homer3 was solved and revealed that all five amino acids cluster at one prominence that is remote from the surface used by Homer to bind polyproline-rich sequences (Fig. 3D) (*7*). We noted a threonine and two serines (Thr^{36}, Ser^{38}, and Ser^{52}) close to the putative NFATc2 binding surface (fig. S6) that are predicted AKT phosphorylation targets (*3*). Indeed, activated AKT (*8*, *9*) prevented the formation of cytoplasmic punctae in cells between Homer2 or 3 and GFP-NFATc2 (fig. S7) and reduced Homer2 and 3 binding to GST-NFATc2 in vitro (Fig. 3, E and F). Mimicking phosphorylation of one or more of Thr^{36}, Ser^{38}, and Ser^{52} reduced NFATc2 binding (fig. S8), whereas the triple alanine mutant (in which Thr^{36}, Ser^{38}, and Ser^{52} are all mutated to Ala) bound NFATc2 and the inhibition by AKT was attenuated (fig. S8). AKT is activated by the CD28 pathway (*10*). CD28 stimulation reduced NFATc2-Homer coimmunoprecipitation from T cells and was AKT-dependent (Fig. 3G). By contrast, treatment with LiCl, a GSK3 inhibitor, did not change the amount of NFATc2 that coimmunoprecipitated with Homer3. These results identify a novel binding surface for Homer and support a model in which CD28/AKT activation reduces Homer3 binding to NFATc2.

To further explore the role of Homer in cooperative activation by CD3 and CD28, we monitored IL-2 expression by T cells isolated from Homer2,3 double-knockout (DKO) mice (*3*) (Fig. 4A). At a threshold concentration for CD3 activating antibody (1 μg/ml), addition of low concentrations of CD28 antibody resulted in IL-2 expression from Homer2,3 DKO greater than from wild-type T cells by a factor of as much as 9 (Fig. 4A). Homer2,3 DKO T cells also showed enhanced proliferation in response to CD3, either alone or with low-dose CD28 antibody (fig. S9, A and B). By contrast, at a high concentration of CD28 antibody, which is not alone sufficient to induce IL-2 production, addition of CD3 antibody resulted in dose-dependent increases of IL-2 production that were identical in wild-type and Homer2,3 DKO T cells (Fig. 4A). Homer2,3 DKO T cells also showed enhanced (versus wild-type) induction of other NFAT-responsive genes to CD3 activation, including IL-4 and interferon-γ (Fig. 4B). Egr-1, which is not NFAT-responsive (*11*), was not differentially induced. IL-2 production and proliferation after T cell activation by antigen-presenting cells (APCs) were similar in wild-type$^{6.5}$ and Homer DKO$^{6.5}$ T cells that express TCRs specific for the influenza hemagglutinin antigen (HA) (Fig. 4C and fig. S9C); however, when CD28 signaling was reduced by pretreatment with CTLA4–immunoglobulin (Ig), Homer2,3 DKO T cells showed a factor of 4 or greater increase in IL-2 production (Fig. 4D). To assay for in vivo effects of APC-dependent T cell activation, we injected cells from Homer2,3 DKO$^{6.5}$ and control transgenic mice into host mice that express the HA antigen on pulmonary epithelial cells (*12*). Mice died more rapidly when they received Homer2,3 DKO$^{6.5}$ T cells than when they received control T cells (Fig. 4E), consistent with enhanced activation of Homer2,3 DKO T cells.

Thymocyte development appeared normal in Homer2,3 DKO mice (fig. S10); however, the percentage of $CD62L^{-}CD44^{high}$ effector-memory T cells in 7- to 10-week-old mice increased by a factor of 2 to 3.5 relative to age-matched wild-type controls (Fig. 4F), suggesting an increase of autoreactive T cells. T_{reg} cells, which suppress T cell activation and are also dependent on calcineurin-NFAT (*13*), were slightly increased in Homer2,3 DKO mice (fig. S11). To assess the long-term effects of Homer2,3 DKO, we examined 14-month-old mice for evidence of immune dysfunction. Homer2,3 DKO mice differed from wild-type mice in having more severe mononuclear infiltrative lesions in the liver (5/5 mild-moderate versus 1/5 mild) (Fig. 4G) and in the lacrimal (Harderian) gland (3/5 moderate-severe versus 0/5) (Fig. 4H), which showed evidence of tissue injury. These changes are similar but less severe than those observed in the Homer3 KO mice in mixed B6/129 background (fig. S1), which suggests that genetic background can affect the phenotype.

Our results support a model in which Homer2 and Homer3 are negative regulators of NFAT-dependent signaling in T cells. NFAT also plays a critical role in calcium-dependent signaling in other cell types, including muscle (*4*) and neurons (*14*, *15*). Interestingly, a *Drosophila* Homer2 homolog was recently identified in a genome-wide RNA interference screen of S2 cells as a negative regulator of NFAT activation (*16*). Our model anticipates that in the resting state, Homer binds NFATc1/c2 together with the Ca^{2+} release apparatus at the immune synapse (fig. S12). In the condition of CD3 monostimulation of T cells, active calcineurin must compete with Homer2,3 for access to NFAT so that only a fraction of NFAT is dephosphorylated and activated. Because calcineurin activity is required to dephosphorylate NFAT, even in the absence of Homer2,3, calcineurin-NFAT signaling is not altered in the basal state (figs. S13 and S14). When CD28 is coengaged, Homer2,3 dissociates from NFAT, leaving greater access for calcineurin to dephosphorylate NFAT1c/2c. We propose that AKT-dependent reversal of Homer's inhibitory function is one means by which CD28 activation enhances IL-2 production. Homer2 is rapidly up-regulated after T cell activation (*17*) (fig. S15), which suggests that the balance of CD3 and CD28 required for activation may be dynamically regulated. Although our analysis of Homer deficient mice revealed a relatively modest phenotype, further exploration using other models may reveal more about Homer proteins in regulating T cell responses. In particular, the role of Homer2,3 in establishment of anergy and responses to natural antigens will be important to examine.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S15
Table S1

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The Frequency Dependence of Osmo-Adaptation in *Saccharomyces cerevisiae*

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The propagation of information through signaling cascades spans a wide range of time scales, including the rapid ligand-receptor interaction and the much slower response of downstream gene expression. To determine which dynamic range dominates a response, we used periodic stimuli to measure the frequency dependence of signal transduction in the osmo-adaptation pathway of *Saccharomyces cerevisiae*. We applied system identification methods to infer a concise predictive model. We found that the dynamics of the osmo-adaptation response are dominated by a fast-acting negative feedback through the kinase Hog1 that does not require protein synthesis. After large osmotic shocks, an additional, much slower, negative feedback through gene expression allows cells to respond faster to future stimuli.

The mechanisms cells use to sense and respond to environmental changes include complicated systems of biochemical reactions that occur with rates spanning a wide dynamic range. Reactions can be fast, such as association and dissociation between a ligand and its receptor (<1 s), or slow, such as protein synthesis (>10^3 s). Although a system may comprise hundreds of reactions, often only a few of them dictate the system dynamics. Unfortunately, identification of the dominant processes is often difficult, and many models instead incorporate knowledge of all reactions in the system. Although occasionally successful (*1*–*4*), this exhaustive approach often suffers from missing information, such as unknown interactions or parameters.

Here, we used systems-engineering tools to study how oscillatory signals propagate through a signal transduction cascade, which allowed us to identify and to model concisely the interactions that dominate system dynamics. The cornerstone of this approach is to measure the cascade output in response to input signals oscillating at a range of frequencies (*5*, *6*). By comparing the frequency response of the wild-type network to that of mutants, the molecular underpinnings of network dynamics can be determined. Studies of neural and other physiological systems have used systems theory (*6*), and control theory has also been applied to cellular networks (*7*–*14*).

We focused on the high-osmolarity glycerol (HOG) mitogen-activated protein kinase (MAPK) cascade in the budding yeast *Saccharomyces cerevisiae*. This cascade forms a core module of the hyperosmotic shock–response system and is particularly well suited to frequency-response analysis for several reasons. First, both the input (extracellular osmolyte concentration) and output (activity of the MAPK Hog1) of the network are easily measured and manipulated. Second, the molecular components of the network have been well studied, which facilitates connecting dynamic models with molecular events. Finally, the system contains multiple negative-feedback loops that operate on different time scales (*4*, *15*, *16*). It is still unclear which negative-feedback loop or loops dominate the signaling dynamics and whether the different feedback loops have distinct biological functions. We determined the properties of the main negative-feedback loops in the HOG network and arrived at a concise predictive model of the signaling dynamics. Furthermore, by analyzing the system's dynamics over a range of osmotic-shock strengths, we begin to understand how the multiple-feedback architecture might be beneficial for osmotic homeostasis in fluctuating environments.

After a hyperosmotic shock, membrane proteins trigger a signal transduction cascade that culminates in the activation of the MAPK Hog1, which is primarily cytoplasmic before the osmo-shock (*17*, *18*). When activated, Hog1 accumulates in the nucleus (Fig. 1A), where it activates a broad transcriptional response to osmotic stress (*19*). Constitutively active phosphatases dephosphorylate and deactivate Hog1, which leads to its export from the nucleus. When osmotic balance is restored, through changes either to the extracellular environment or to the intracellular osmolyte concentration, cascade activity ceases, and the Hog1 nuclear enrichment decreases (Fig. 1A). To estimate the amount of phosphorylated Hog1 in living cells, we simultaneously monitored the cellular localization of Hog1-YFP, a yellow fluorescent protein fused to Hog1, and Nrd1-RFP, a red fluorescent protein fused to a strictly nuclear protein. To quantify Hog1 nuclear localization, we define the function, $R(t) = (\langle YFP \rangle_{nucleus} / \langle YFP \rangle_{cell})_{population}$, as the ratio (averaged over many cells) of mean YFP pixel intensities in the nucleus and the whole cell [(Fig. 1A), red circles].

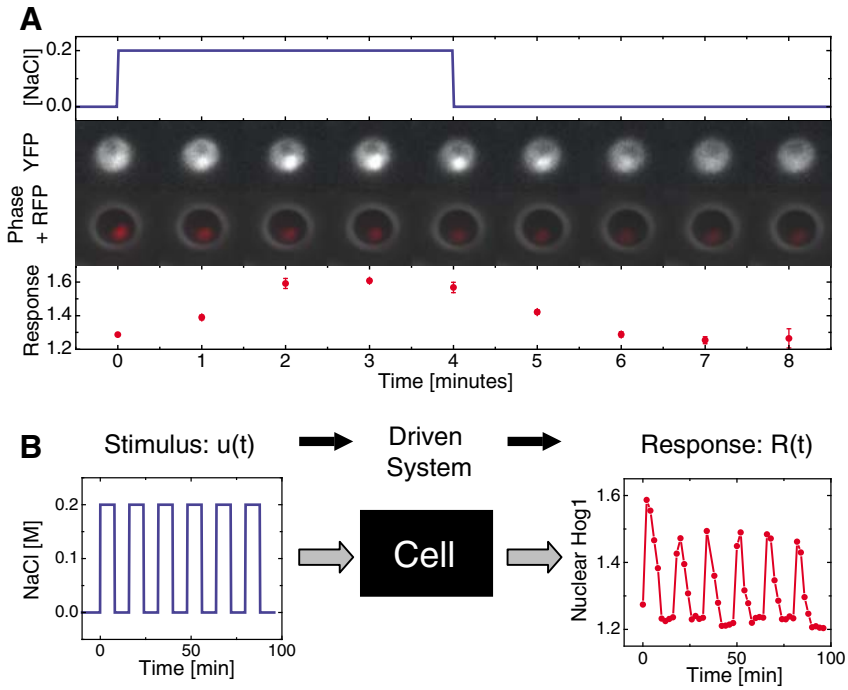

Fig. 1. Enrichment of Hog1 nuclear localization is driven by pulsed salt shocks. (**A**) Localization of the fusion protein Hog1-YFP and the nuclear marker Nrd1-RFP by fluorescence microscopy. We applied and removed NaCl (0.2 M) as shown by the blue line. The population average translocation response (red circles) was defined by the ratio of average YFP fluorescence in the nucleus to the average whole-cell YFP fluorescence. (**B**) Oscillations of Hog1-YFP translocation in a population of cells (red circles) in response to square-wave oscillations in the input of extracellular NaCl (blue line).

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Cells were periodically shocked in a flow chamber (fig. S1) in which a computer-actuated valve supplied square-wave pulses of medium, with and without 0.2 M NaCl [(Fig. 1B), blue line]. Localization of fluorescent proteins was concurrently imaged [(Fig. 1B), red circles]. Using Fourier analysis (*20*), we approximated both the input and output signals as sine waves oscillating with a period $T_0 = 2\pi/\omega$ and quantified the output signal by the magnitude of the amplitude (A) at the driving frequency $A(\omega)$ and the relative phase shift $\phi(\omega)$ (Fig. 2A) (*21*). We measured the response of the system to square-wave stimuli with periods ranging from $T_0 = 2$ min to $T_0 = 128$ min (fig. S2). These responses were analyzed to obtain so-called Bode plots (Fig. 2, B and C) (*20*), representing the frequency-dependent amplitude $A(\omega)$ and phase $\phi(\omega)$.

We used linear-systems theory to develop a predictive model for the response to arbitrary osmotic input signals $u(t)$ (*20*). We fitted a general second-order linear time–invariant (LTI) model to the data in Fig. 2B and used the extracted parameters and a simple nonlinear element (*20*, *22*) to predict the response to a step input of 0.2 M NaCl. The model accurately predicted both the response amplitude and the time required to return to basal activity [(Fig. 2D), blue circles].

Because our model was not instructed by knowledge of the underlying biology, we sought to explore how it is similar to and different from the canonical molecular model of the hyperosmotic-shock response. Thus, we converted our LTI model into a model that is more readily interpreted in terms of biological processes (*20*):

$$\dot{y} = (A_0 u - x) - \gamma y$$
$$\dot{x} = \alpha(A_0 u - x) + \beta y \quad (1)$$

This model contains two negative-feedback loops, which act to reduce the difference, $(A_0u - x)$, between the stimulus A_0u and the internal-state variable x. Fig. 3A shows a schematic of the model, and Fig. 3B shows the canonical bio-

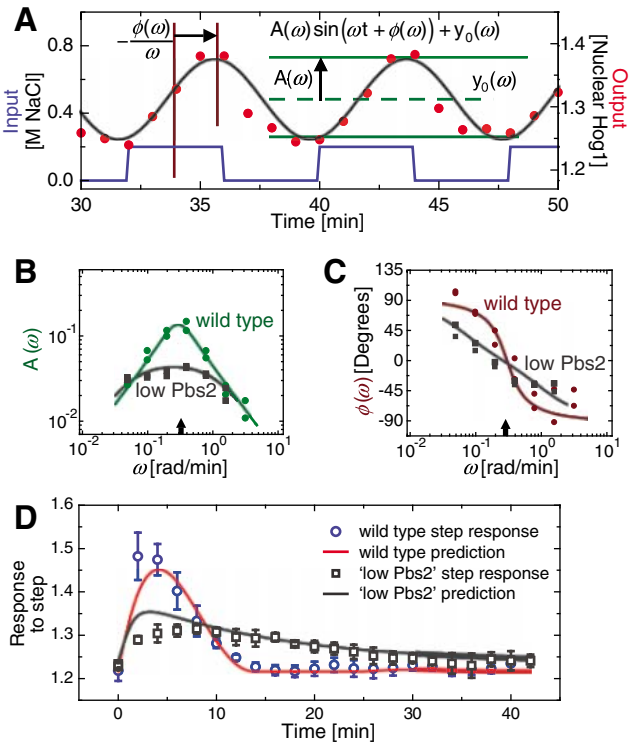

Fig. 2. Fourier analysis, model fits, and model predictions of Hog1 nuclear enrichment. (**A**) Illustration of the input (NaCl concentration, blue line), the network response (Hog1-YFP translocation, red circles), and the sine wave (black line) corresponding to the Fourier component of the response at the driving frequency ω. This Fourier component is described by three parameters: $A(\omega)$ (green) representing the amplitude of the oscillations, $\phi(\omega)$ (brown) representing the phase delay between the input and the response oscillations, and $y_0(\omega)$ representing the signal offset. (**B**) Measurement of the Fourier amplitude $A(\omega)$ (green dots) over a range of driving frequencies along with model fit (green line). (**C**) Phase of the response measured relative to the driving signal (brown dots) along with model prediction of the phase (brown line). (**D**) Response of the system to a step increase of 0.2 M NaCl compared with the step response predicted by the model. The "low Pbs2" data (boxes) are gathered from the Pbs2 underexpressing mutant strain and were used to generate the model fit [gray line in (B)] and model predictions [gray lines in (C) and (D)].

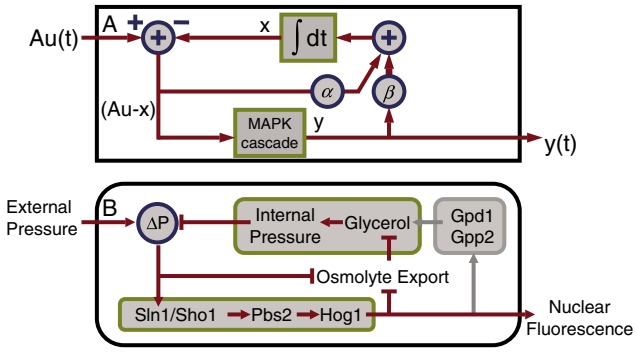

Fig. 3. Network topology implied by pulsed-input analysis corresponds to biological network. (**A**) Diagrammatic representation of the mechanistic model shows two linear negative-feedback responses: one dependent on Hog1 activity with strength β and a second independent of Hog1 activity with strength α. The intracellular osmotic pressure was modeled as an integrator, whereas the MAPK signal transduction pathway was modeled by the linear impulse–response function. The output of circumscribed-plus-sign symbols is simply the sum of its inputs. (**B**) The osmo-adaptation network structure. With the inducement of osmotic stress, cells increase or decrease their export rate of glycerol through the transmembrane protein Fps1, which is modified by Hog1-independent and Hog1-dependent mechanisms. In addition, under high osmotic stresses, active nuclear Hog1 is known to modify the expression of glycerol-producing proteins over longer time scales. ΔP represents the difference between internal and external pressure relative to its optimal value.

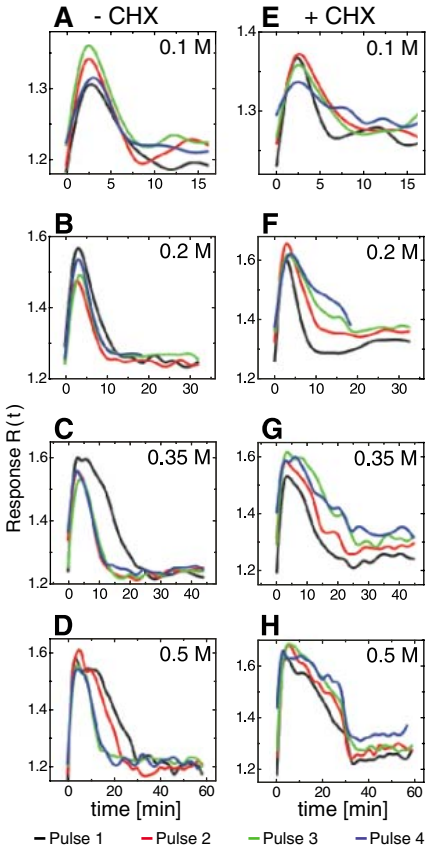

Fig. 4. Gene expression facilitates response to subsequent pulses. Consecutive-pulse responses were compared for cells treated with (**A**) 0.1 M NaCl, 16-min period (i.e., 8 min at 0.1 M followed by 8 min at 0.0 M); (**B**) 0.2 M NaCl, 32-min period; (**C**) 0.35 M NaCl, 45-min period; and (**D**) 0.5 M NaCl, 60-min period. (**E** to **H**) Similarly treated cells also exposed to cycloheximide.

chemical mechanisms that regulate the osmotic-shock response. Because of the high degree of correspondence between our derived model and the extensive Hog1 literature, we interpret the state variable, x, as the intracellular osmolyte concentration and y as enrichment of phosphorylated Hog1 above its baseline level. Thus, interpreted in biological terms, our model predicts that one feedback pathway depends on Hog1-induced glycerol accumulation (i.e., βy changes x through the activity of the observable y), whereas a second glycerol-accumulating pathway is Hog1-independent [i.e., $\alpha(A_0 u - x)$ changes x independently of y].

To gauge the relative strength of the two feedbacks, we applied the same Fourier technique to a mutant strain expressing a reduced amount of Pbs2, the MAPK kinase that phosphorylates Hog1 (Fig. 3B). Because Hog1 is not activated as highly after a hyperosmotic shock in this strain, we can effectively isolate Hog1-dependent feedback from Hog1-independent feedback by comparing the response dynamics (fig. S4) to those of the wild-type strain. Bode plots for this strain were different from those of the wild-type strain (Fig. 2, B and C). Matching the LTI model to the $A(\omega)$ data alone yielded a good fit [(Fig. 2B), black squares], as well as an accurate prediction for the $\phi(\omega)$ data [(Fig. 2C), black squares] and the step response [(Fig. 2D), boxes]. The latter prediction [(Fig. 2D), gray line] reproduced both the reduced maximum response and the slower response dynamics observed in this strain. This suggests that the Hog1-dependent feedback loop plays a major role in rapidly regulating the osmotic-shock response (*20*).

We compared our model with known biological details of the hyperosmotic-shock response (*4*, *15*, *16*). Yeast regulate their intracellular osmolyte concentration through two parallel mechanisms. In a Hog1-independent manner, the membrane protein Fps1 quickly (<2 min) responds by decreasing the glycerol-export rate (*23*, *24*), thereby leading to glycerol retention. Further, active Hog1 increases expression of the glycerol-producing proteins Gpd1 and Gpp2. This raises the intracellular glycerol level over longer time scales (>30 min) (*25*).

Although the topology of our derived model corresponds closely to that of the known biological system (Fig. 3, A and B), dynamic differences suggest that the current view of the MAPK's role in osmotic regulation is incomplete. Cells begin to recover from the NaCl pulse within 5 min and are finished responding within 15 min. Both of these time scales are faster than required for gene expression, which is typically greater than 15 min (*4*). This suggests that both feedback loops in our model control the rapid accumulation of glycerol, consistent with previous reports (*23*, *24*, *26*).

Our model suggests that gene expression plays a minimal role in the hyperosmotic-shock response, yet the expression of hundreds of genes changes in response to hyperosmotic shock. We hypothesized that gene expression may be more important as a longer–time scale feedback in this system, so we looked for pulse-to-pulse variability in the response of cells stimulated with periodic pulses of NaCl (fig. S5). Cells were shocked either in the absence (Fig. 4, A to D) or presence (Fig. 4, E to H) of cycloheximide, a small molecule that inhibits protein synthesis. As predicted by the initial data, cells responded very similarly to an initial pulse of osmolyte regardless of their ability to synthesize new proteins (Fig. 4, black lines). Nevertheless, we found that cells stimulated multiple times recovered from each subsequent pulse faster in the absence of cycloheximide and slower in its presence, revealing a longer–time scale component absent from our earlier data. These results suggest that nontranscriptional feedback mediates short–time scale osmolyte accumulation (*4*, *16*, *26*, *27*), whereas gene expression plays a role in osmolyte production only on longer time scales and for more intense shocks. Accordingly, we found that stronger shocks cause cells to increase their rate of glycerol production (fig. S6) in a manner that depends on gene expression, which permits faster recovery to subsequent fluctuations (*28*).

These results demonstrate the promise of applying engineering principles to cellular networks, particularly when predicting the response of the system to dynamic stimuli. In more complex systems, measuring the activity level of all relevant state-space variables could help with determining the effective network structure.

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20. Details are available in the supporting materials on *Science* Online.
21. In principle, both the input and output signals also contain higher-frequency components. Nevertheless, here we focus on the driving frequency alone in order to simplify analysis while obtaining significant information about the signal's strength and timing.
22. The linear model is related to measured outputs using the formulas $R_{\mathrm{model}}(t) = f_{\mathrm{nl}}[y(t)] + R_0$ and $f_{\mathrm{nl}}(y) = y(t) + |y(t)|$ (fig. S3).
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Supporting Online Material

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Please join us in Boston,
David Baltimore, Ph.D.
AAAS President
Robert Andrews Millikan Professor of Biology
California Institute of Technology

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Opening Ceremony

President's Address

David Baltimore, Ph.D.

AAAS President; Robert Andrews Millikan Professor of Biology, California Institute of Technology

Baltimore is one of the world's leading biologists and a co-recipient of the 1975 Nobel Prize in Medicine for the discovery of reverse transcriptase. Since then, he has published more than 600 papers, including seminal research on the genetics of cancer, the workings of the HIV virus and AIDS vaccine candidates, and fundamental observations in molecular immunology. He was founding director of the Whitehead Institute for Biomedical Research and president of Rockefeller University and Caltech. Today he heads the Baltimore Lab at Caltech, with support from the Gates Foundation, to look for ways to genetically boost the immune system against infectious pathogens, particularly HIV. Throughout his career, Baltimore has influenced science policy. He helped set standards for recombinant DNA technology and received the 1999 National Medal of Science in part for his work on AIDS research policy. Today he is outspoken about what he sees as government efforts to distort and suppress scientific research.

Invited Address

His Excellency Paul Kagame

President of the Republic of Rwanda

Born in October 1957 in Ruhango, Southern Province, Kagame's family fled Rwanda in 1960 to escape persecution and ethnic programs that characterized the nation in subsequent decades. In 1990, he returned after 30 years in exile to lead the Rwandan Patriotic Army (RPA) in a liberation struggle that succeeded in 1994. In 2000, he was unanimously elected President by the Transitional National Assembly, and three years later, he became the first democratically elected President of Rwanda. Confronting deep poverty and the aftermath of genocide, Kagame has demonstrated his strong support of plans to pursue sustainable development that are built on science and education to achieve growth and prosperity. He has received achievement awards and international recognition for uniting and reconciling Rwandans, promoting the use of Information and Communication Technologies for the overall development of the African continent, furthering gender mainstreaming and addressing social and cultural barriers that impede the involvement and advancement of women in national affairs, and abolishing the death penalty.

Plenary Lectures

Nina V. Fedoroff, Ph.D.

Special Adviser, Science and Technology, U.S. Department of State
Evan Pugh Professor of Biology and Willaman Professor of Life Sciences, Huck Institutes of the Life Sciences, Pennsylvania State University
Making the World Flat: Science and Technology in the Developing World

In August 2007, Fedoroff was named the Science and Technology Adviser to U.S. Secretary of State Condoleezza Rice. She holds an academic post as the Evan Pugh Professor of Biology and Willaman Professor of Life Sciences at Pennsylvania State University, where she is also founding director of the Huck Institutes of the Life Sciences. As a leading geneticist and molecular biologist, she has contributed to the development of modern techniques used to study and modify plants. Her book, *Mendel in the Kitchen: A Scientist's View of Genetically Modified Foods*, examines the scientific and societal issues surrounding the introduction of genetically modified crops. She received the 2006 National Medal of Science for her pioneering work on plant molecular biology and for being the first to clone and characterize maize transposons.

Nicholas Negroponte, Ph.D.

Founder, One Laptop per Child
One Laptop per Child

Negroponte is founder and chairman of the One Laptop per Child non-profit association. He is currently on leave from MIT, where he was co-founder and director of the MIT Media Laboratory, and the Jerome B. Wiesner Professor of Media Technology. A graduate of MIT, Negroponte was a pioneer in the field of computer-aided design, and has been a member of the MIT faculty since 1966. Conceived in 1980, the Media Laboratory opened its doors in 1985. He is also author of the 1995 best seller, *Being Digital*, which has been translated into more than 40 languages. In the private sector, Negroponte serves on the board of directors for Motorola Inc., and as general partner in a venture capital firm specializing in digital technologies for information and entertainment. He has provided start-up funds for more than 40 companies, including *Wired* magazine.

Judith Rodin, Ph.D.

President, Rockefeller Foundation
Climate Change Adaptation: The Next Great Challenge for the Developing World

Rodin trained as a research psychologist and was the first woman to serve as president of an Ivy League institution, the University of Pennsylvania. A pioneer in the behavioral medicine movement, she also taught at New York University before joining the faculty at Yale and then becoming provost. Today she leads the Rockefeller Foundation,

established in 1913 by John D. Rockefeller Sr., to "promote the well-being" of humanity by addressing the root causes of serious problems. The Foundation works around the world to expand opportunities for poor or vulnerable people and to help ensure that globalization's benefits are more widely shared. With assets of nearly $4 billion, it is one of the few institutions to conduct such work both within the United States and internationally. Rodin serves on several leading nonprofit and corporate boards. She has written or co-written 12 books, including most recently *The University and Urban Revival*. She served on President Clinton's Committee of Advisors on Science and Technology. A member of several leading academic societies, including the Institute of Medicine of the National Academy of Sciences, she has received 14 honorary doctorate degrees.

Plenary Panel
Global Health Challenges

AAAS President David Baltimore, moderator

JIM YONG KIM

Jim Yong Kim, M.D., Ph.D.
Director, François Xavier Bagnoud Center for Health and Human Rights, Harvard School of Public Health, and Professor of Social Medicine and Medicine, Harvard Medical School

Peter Piot, M.D., Ph.D.
Executive Director, UNAIDS, and Under Secretary-General of the United Nations

UNAIDS/O.O'HANLON

PETER PIOT

Timothy Wirth, Ph.D.
President, United Nations Foundation and Better World Fund

TIMOTHY WIRTH

AAAS President Baltimore will moderate a Davos-style panel discussion that explores global health challenges from three perspectives: philanthropy, world leadership, and program successes and challenges. Executive director of UNAIDS since its creation in 1995 and under secretary-general of the United Nations, Piot comes from a distinguished academic and scientific career focusing on AIDS and women's health in the developing world. Drawing on his skills as a scientist, manager, and activist, he has challenged world leaders to view AIDS in the context of social and economic development as well as security. Kim has worked to improve health in developing countries for more than 20 years and is an expert in tuberculosis. He is a founding trustee and the former executive director of Partners In Health, a not-for-profit organization that supports a range of health programs in poor communities in Haiti, Peru, Russia, Rwanda, and the United States. Following two decades of elected politics in the U.S. Congress, Wirth served in the U.S. Department of State as the first Undersecretary for Global Affairs. Since 1998, he has organized and led the formulation of the United Nations Foundation's mission and program priorities. The Foundation also engages in extensive public advocacy, resource mobilization, and institutional strengthening efforts on behalf of the UN.

Topical Lectures

Angela M. Belcher, Ph.D.
Germeshausen Professor of Materials Science and Engineering and Biological Engineering, Massachusetts Institute of Technology
From Nature and Back Again: Giving New Life to Materials for Energy, Electronics, and the Environment

Janet Browne, Ph.D.
Aramont Professor of the History of Science, Harvard University
2008 George Sarton Award Lecture in the History and Philosophy of Science
Commemorating Darwin: The History of Scientific Celebrations

Charles Elachi, Ph.D.
Director, NASA Jet Propulsion Laboratory
The Golden Age of Robotic Space and Earth Exploration: Challenges and Opportunities

Daniel Kahneman, Ph.D.
Eugene Higgins Professor of Psychology, Princeton University
2008 John P. McGovern Lecture in the Behavioral Sciences
Architecture of the Mind

Curtis T. McMullen, Ph.D.
Cabot Professor of Mathematics, Harvard University
The Geometry of 3-Manifolds

Per Pinstrup-Andersen, Ph.D.
H.E. Babcock Professor of Food, Nutrition, and Public Policy, Cornell University
Science and Policy Priorities for the Global Food System

Lawrence Susskind, Ph.D.
Ford Professor of Urban and Envioronmental Planning, Massachusetts Institute of Technology
Strengthening the Global Environmental Treaty-Making System

Nathan D. Wolfe, Ph.D.
Professor of Epidemiology, UCLA School of Public Health
Viral Forecasting

Topical Panel
Advancing Science and Fostering Innovation Through International Cooperation: A Trans-Atlantic Perspective

AAAS President David Baltimore, moderator

Mark Fishman, M.D.
President, Novartis Institutes for BioMedical Research

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- Forum for Sustainability Science Programs
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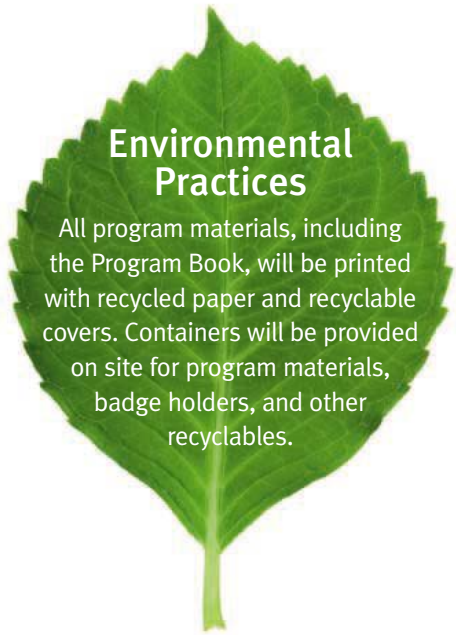

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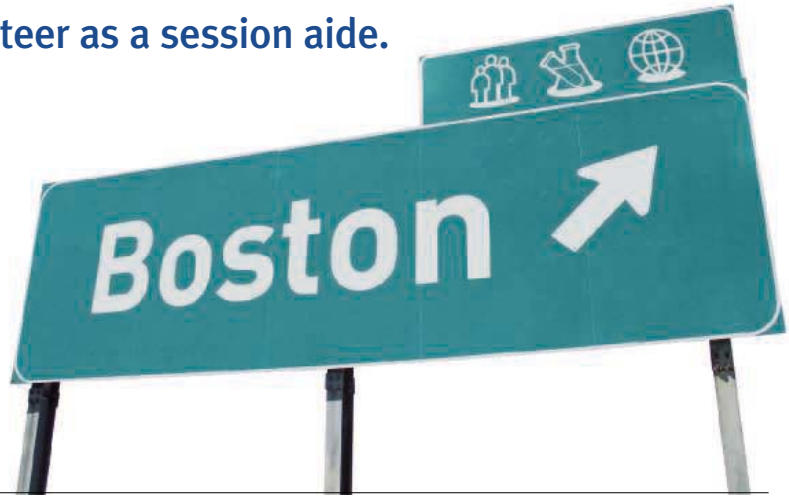

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- Is it the fat, the carbohydrates, or the calories?
- What does science tell us about children's nutritional needs worldwide?
- Is there enough time in the school day for exercise?
- How can nutrition instruction fit into the K-12 science curriculum?
- What roles can communities, schools, culture, and people play in addressing the problem of childhood obesity?

Program updates and more information will be available at www.aaas.org/obesity.

2008 Forum for School Science
Programs that Create a New Science Professional: The Ph.D. as Public Educator

What do Georges Charpak, Russell Hulse, Leon Lederman, and Carl Wieman have in common aside from physics and the Nobel Prize? All are research scientists who are engaged in K-16 science education.

What motivates science professionals to get involved in science education and to engage in collaborations with an individual teacher, a school, a school system, or a science organization in the community? The 2008 Forum for School Science will:

- Describe selected collaborations and partnerships between universities and school systems,
- Provide steps for developing and sustaining the partnerships,
- Describe the value added for the institutions and individuals involved, and
- Offer data and analyses from projects and outside evaluators on the effectiveness of the program and the impact on graduate students, teachers, the universities, and the school systems.

The Forum will highlight programs that build partnerships between institutions of higher education and school systems to promote improvements in science, technology, engineering, and mathematics education, and engages a new generation of scientists to communicate their research to the public.

2008 Seminar
Managing Threats to Marine Ecosystems

Organized by: **Larry Crowder, Duke University, Beaufort, N.C.**
This two-day seminar focuses on threats to marine ecosystems, first describing the location and magnitude of those threats based on new spatially-explicit analyses. New sensing technologies and new analytical tools map the effects of human activities on marine resources as well as collateral damage to habitats and non-target species.

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Attendees will hear about a variety of new discoveries and novel methodologies that will fuel the development of marine ecosystem-based management.

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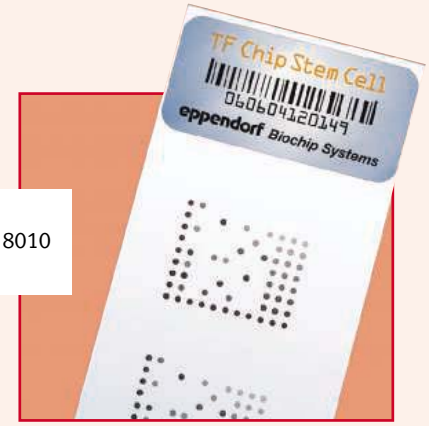

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FACULTY POSITIONS

CHAIR
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Western University of Health Sciences College of Pharmacy invites applications for the position of Chair, Department of Pharmaceutical Sciences.

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Western University seeks applicants of distinguished academic and administrative accomplishments who possess a passion for excellence and can illustrate a proven record of achievement.

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The review of applications will begin immediately and continue until the position is filled. Interested applicants should: (1) submit a letter of intent including leadership and research accomplishments, (2) submit their curriculum vitae, and (3) arrange to have three letters of recommendation sent to the **Search Committee Chair**. Electronic submission of all appropriate materials is preferred and encouraged.

Send application material to: **Stephen A. O'Barr, Ph.D., Chair, Search Committee, Western University of Health Sciences, College of Pharmacy, 309 E. Second Street, Pomona, CA 91766. Telephone: 909-469-5643; fax: 909-469-5600; e-mail: sobarr@westernu.edu.** College **website: http://www.westernu.edu/pharmacy.**

Western University of Health Sciences is an Equal Opportunity/Affirmative Action Employer and actively seeks applications from women and minorities.

TENURE-TRACK ANATOMY FACULTY POSITION
University of Wisconsin, Madison

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FACULTY POSITIONS

HEAD, DEPARTMENT of GENETICS
North Carolina State University
Raleigh, North Carolina

The Department of Genetics at North Carolina State University invites nominations and applications for the position of Department Head. We seek an individual with outstanding leadership capabilities, proven academic and administrative experience, the vision to build and sustain programs at the forefront of genetics research, and a commitment to excellence. Candidates will be expected to maintain an externally funded, high-impact research program. The position announcement can be viewed in its entirety on the Department of Genetics **website: http://www.cals.ncsu.edu/genetics/.**

Applicants should submit a letter of interest, curriculum vitae, statement of philosophy/vision as a Department Head to include research and teaching functions, and three to five representative publications electronically to **website: http://ncsu.edu/jobs/.**

Position number 01-64-0714. Nominations and questions concerning this position should be sent to: **Damian Shea, Chair, Genetics Head Search Committee, Department of Zoology, Campus Box 7617, North Carolina State University, Raleigh, NC 27695-7617,** or via **e-mail: d_shea@ncsu.edu**. Review of applications will begin 15 February 2008, and continue until the position is filled. *Affirmative Action/Equal Opportunity Employer. North Carolina State University welcomes all persons without regard to sexual orientation.*

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Seeking the Skills for a Successful Career in Academia

To many on the outside, life as a tenured faculty member conjures up images of dreamy afternoons spent theorizing at one's desk, interspersed with occasional trips to the lab to hold up test tubes to the light. Of course, anyone who's been to grad school for more than a week knows there's more to scientific endeavor than that. In fact, a faculty member's requisite skill set is quite extensive. **By Emma Hitt**

Tenure-track faculty members must not only think well, but they must also write well, speak well, and interact with people well. They should have a keen business sense and be adept in managing budgets, projects, and people. Paradoxically, they must be fiercely independent, yet able to collaborate well with others. They must be confident enough to know when they've found a scientific truth, but humble enough to admit when they are wrong. They should be kind enough to mentor younger scientists, but stingy enough with their time to be able to manage it well. In addition, faculty members must have a driving passion toward their research and be willing to devote a Herculean effort over many years. Despite these stringent requirements, many can and do succeed in academia. The key, it seems, is making a conscientious effort to develop the necessary skills early on. In this article, people who have achieved high levels of success in academia provide specific, practical advice to others who would follow in their path.

Passion—Fuel That Fans Flames of Success

One resounding theme from successful faculty members is that one has to have passion. This is something that cannot be feigned, learned, or coerced—it either exists or it does not. "There has to be an inherent interest, whether it is derived from a crystalizing experience such as a parent dying of cancer, or from a value system that has developed within a person," says **Mary Delong,** director, Office of Postdoctoral Education at Emory University, which oversees career development for nearly 500 postdoctoral fellows. In addition to cultivating a passion for one's work, Delong also mentions that during the postdoc years, developing a track record of performance through publishing papers and fully researching opportunities in the field are probably the most important steps. "But passion is what will carry a postdoc through the challenges," she says.

Joseph Coyle, with Harvard Medical School, who has studied schizophrenia and other neurological disorders for more than 40 years, was drawn into his career path early on. "I'd say for most of my life I never saw myself as going to work, I saw myself as going to do something I totally enjoy," he says. "If it's drudgery, you ought not do it. But if research isn't your passion, then a Ph.D. can afford many different opportunities, such as patent law and science writing. You don't have to feel trapped."

Standing upon the Shoulders of Giants

A large proportion of Ph.D.s in the sciences go on to seek a postdoc position—about 77 percent of Ph.D.s in the biological sciences and 61 percent in the physical sciences, according to a 2006 National Science Foundation report. One of the first steps in graduate school and beyond is to seek out mentors who will provide guidance but who will also foster independence, says **Nancy Schwartz,** who conducts research on proteoglycan synthesis at the University of Chicago. Schwartz states that, for better or worse, she was forced into thinking independently early on during her career because of the intermittent absences of her thesis and postdoctoral advisers. She doesn't recommend that as a situation to seek out, "but really, it is each individual's responsibility to garner what they think they need from many other colleagues and mentors, throughout their career."

Story Landis, director of the US National Institute of Neurological Disorders and Stroke (NINDS), who was in academic research for many years, also recommends continued »


Mary Delong


Nancy Schwartz

"It is each individual's responsibility to garner what they think they need from many other colleagues and mentors."

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Diversity: Women in Science—Februrary 8

Postdoctoral Scientists 1—Februrary 22

Careers in Preclinical Drug Discovery and Development (online only)—March 7

"Science is too dangerous to do alone—too daunting, too lonely, and too huge."
—William Mobley

being assertive about seeking out opportunities for oneself. "Early on in my career, senior people often gave me the opportunity to write reviews or to speak at meetings, and this really helped develop my skills."

However, both Schwartz and Landis point out that one has to be careful about taking on too many administrative duties that would interfere with lab and teaching duties—this, they say, is especially important for women and minorities to remember, since they are frequently unrepresented on panels and often asked to participate in this way.

William Mobley at Stanford University suggests avoiding administrative responsibilities when possible, "except those you think would be fun to do and that would directly benefit your career and your science, such as participating in grant reviews—there will be more time to focus on these types of responsibilities later on," he says.

No Man (or Woman) Is an Island

Another key component of a successful academic career is the ability to establish collaborations with other researchers and learning to depend on the help of others. This, of course, can be especially challenging for young scientists who, in the crucible that is graduate school, slowly come to achieve academic independence. Mobley, however, advises postdocs and junior faculty to seek out collaborations. "Science is too dangerous to do alone—too daunting, too lonely, and too huge," he says.

"As you transition from being a postdoc to having your own lab, you start to rely on other people and their efforts more and more," notes **Richard Bucala,** a researcher in rheumatology at Yale. "One should never be afraid about hiring or collaborating with somebody who is smarter. I think that's the only way that one can really advance and grow."

Tenure-Track

According to the Howard Hughes Medical Institute, a tenure-track position is one that leads to a permanent professorial appointment and potentially full salary support if grant funding runs out. A faculty member can be fired only for limited reasons, such as gross misconduct. In general, a tenure-track faculty member will hold a position for about five years before a formal decision is made on whether tenure will be granted.

In 2003, among science and engineering doctoral degree holders who received their degrees within the past four to six years, approximately 20 percent were in tenure-track or tenured positions at four-year institutions of higher education, according to a National Science Foundation report. The percentage rates for individuals in various degree fields are as follows: Engineering 16.3; Life Sciences 18.0; Physical Sciences 16.7; Social Sciences 30.8.

Dennis Liotta, whose lab at Emory identified the HIV drug emtricitabine, advises postdocs and junior faculty to find some colleagues that they respect, and make it their business to develop a genuine and collegial relationship with them. "These relationships should also extend out of the university and into other labs and institutions to provide a fresh perspective," he says.

Winning at the Lab Business

An important transition period is moving from being a postdoc to starting one's own lab, which presents a set of novel challenges. Mobley suggests that people signing up for an assistant professorship seek a position where the salary and necessary startup equipment costs are covered for at least a full three years. "If they can't offer you that, then they don't want you enough, and that's not the place to go," he notes.

Regarding salary, according to a 2006-07 survey by the American Association of University Professors, salaries for full-time faculty averaged $73,207. By rank, the average was $98,974 for professors, $69,911 for associate professors, $58,662 for assistant professors, $42,609 for instructors, and $48,289 for lecturers, although these figures are not specific for the sciences.

Managing a lab is really managing a small business and these are skills that, for the most part, are not taught in graduate school or during a postdoctoral position, Schwartz says. "You're managing people and budgets, and you're seeking funding, and then you're responsible for how those funds are spent." She recommends taking at least a few days to learn about budgeting, and mapping out a projected budget of what everything is going to cost. "Some of our junior faculty are totally astounded when they see how fast grant or startup money goes because they have not really considered the costs," she says.

When it comes to managing people, lab tech and postdoc underlings are going to look to the leader of the lab, i.e., the new junior faculty member, to set the standard for that lab. "Whatever time in the lab that you set for yourself, that will tend to be the standard," says Liotta. "So, if you want people to work evenings and weekends, then you will have to show up then also. Good students will often show up regardless, but that extra motivation of having their boss there is helpful."

It's also important to seek out the kind of staff, such as students and postdocs, that will meet expectations, Schwartz advises. "You have to be explicit about your expectations; if you plan on working 15 hours a day in the beginning, then you want a lab staff that will be willing to match that lifestyle." You also have to learn to let go and let people make mistakes, "otherwise, you're not going to allow people to become independent thinkers and doers. They're going to develop more of a 'technician' mentality."

Creative Funding Strategies

A primary stressor that affects even seasoned faculty is funding. Coyle points out that when NIH funding is more difficult to obtain, as it is now, the most creative science, or science from younger faculty, may sometimes be passed over in favor of the less risky, or the tried and true.

However, Landis notes that the NIH has committed to fund as many first time R01 applicants in 2007 and again in 2008 as the average of the past five years. "NINDS funded R01s to the 25th percentile while experienced investigators were guaranteed funding continued »

MATERIALS SCIENCE & ENGINEERING

CONNECTIONS: Louisiana State University (LSU, www.lsu.edu) is seeking to strengthen its connections between faculty engaged in basic discovery and applied scientific/engineering fields by actively recruiting leaders in scholarship, research, and teaching from the academic, private and governmental sectors. Building on a strong interdisciplinary tradition, we proudly introduce the Materials Science and Engineering Multidisciplinary Hiring Initiative (MHI).

The MHI is being led by the Departments of Chemical Engineering, Chemistry, Electrical & Computer Engineering, Mechanical Engineering, and Physics & Astronomy along with several major interdisciplinary research centers located on the LSU campus, such as the Center for Advanced Microstructures and Devices (CAMD), Center for Computational Technology (CCT) and the Center for BioModular Multi-Scale Systems (CBM2). The Materials Science and Engineering MHI is soliciting applications to fill seven faculty positions with appointments in any of the aforementioned departments. Established leaders in scholarly activities related to materials research (broadly defined) will be recruited along with faculty at the entry level(s). All areas of materials research will be considered, and we expect to hire experimentalists and theorists. Examples of emphasis areas include:

1. Solid-state synthesis, fabrication and characterization – low dimensional material design and investigation employing techniques such as (but not limited to) neutron, X-ray, and optical spectroscopies.

2. Theoretical materials science – analytical and computational approaches to generate a fundamental basis for the design of materials from the macroscopic to the nanoscale, as well as predicting and understanding their behavior starting from a microscopic approach.

3. Electron microscopy – scientists/engineers developing new techniques and/or image processing algorithms for interrogating both hard and soft materials using high resolution TEM, SEM or cryo-EM.

4. High performance polymer synthesis – Meso-scale to nano-scale polymer design leading to functional and responsive materials, conducting polymers, catalysts to control polymerization architecture, or building new monomeric units.

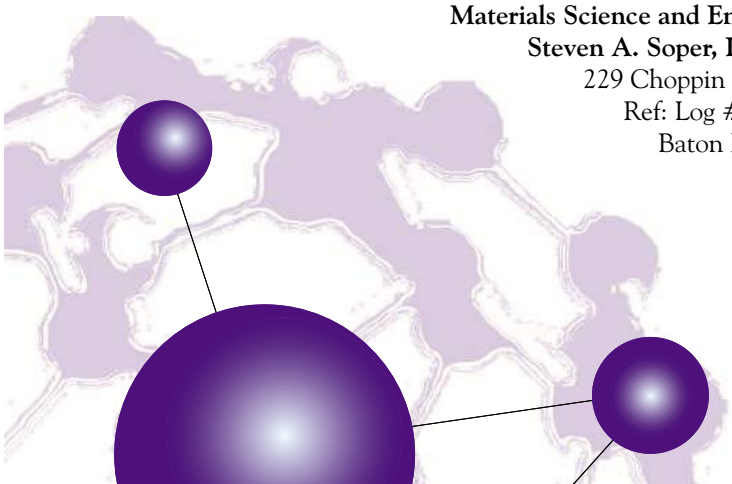
5. Nanoscale devices and systems – Materials and their applications to molecular-scale electronics, nanofabrication, and micro-/nano-electro-mechanical systems (MEMS/NEMS).

Qualified candidates must hold a Ph.D. degree or equivalent in materials science and engineering, or a related discipline (such as Applied Mathematics, Chemistry, Engineering or Physics). Successful candidates at all levels must possess a distinguished record of research accomplishments and publications. They will be expected to build a strong research program and attract extramural funding, lead independent research at the cutting edge of their field, teach courses at all levels, supervise graduate students in scholarly activities and contribute to economic development efforts.

Candidates are invited to submit an application package, which should include a cover letter, curriculum vitae and the names/addresses of at least three references, to the mailing address listed below. The Search Committee will commence the evaluation of applications in March, 2008. An offer of employment is contingent on a satisfactory pre-employment background check.

LSU is an Equal Opportunity/Equal Access Employer. Applications from women and under-represented minorities are strongly encouraged.

Materials Science and Engineering Multidisciplinary Hiring Initiative
Steven A. Soper, Ph.D., Search Committee Chair
229 Choppin Hall, Louisiana State University
Ref: Log #1111
Baton Rouge, LA 70803



LSU

LSU Research: ***The Constant Pursuit of Discovery***
www.lsu.edu/research
www.mhi.lsu.edu/materialsscience

"There is a lot more foundation money out there than there was when I started out."
—Joseph Coyle

if they got a 9th percentile, and overall we funded 15 percent of research project grants," she noted.

Coyle suggests seeking out alternate funding sources such as various foundations or nonprofits. "There is a lot more foundation money out there than there was when I started out," he says. "I think even basic science, even someone who's going to be doing basic biological research should think about the potential clinical applications and should look for opportunities to get support from relevant foundations that are interested in the clinical aspects of the research."

Bucala also advises young faculty to think outside the box when it comes to defining their research. "One has to be opportunistic. If one is really, for instance, captivated by the biochemistry of protein kinases, you don't necessarily have to work on kinases in oncogenesis. You can work on them as they relate to learning and memory or host defense mechanisms. You can't let yourself be constrained necessarily by a particular application," he says.

However, Liotta advises staying away from a "brute force approach" to getting funded. "The most important aspect for getting funding is putting together a well-thought-out proposal," he says. Liotta also suggests waiting to get results that are sufficiently compelling and provocative, and are likely to get the attention of the study section. "If they see a mediocre proposal from you several times, then they're going to associate you with mediocre science."

Emory University
www.emory.edu

Emory University, Office of Postdoctoral Education
med.emory.edu/postdoc/CurPostdoc/index.cfm

Harvard Medical School
www.hms.harvard.edu

NINDS, US National Institutes of Health
www.ninds.nih.gov

Stanford University
www.stanford.edu

University of Chicago
www.uchicago.edu

Yale University
www.yale.edu

Additional Resources:

American Association of Medical Colleges mentoring guidelines
www.aamc.org/research/postdoccompact/

American Association of University Professors
www.aaup.org

National Postdoctoral Association
www.nationalpostdoc.org

National Science Foundation
www.nsf.gov and www.nsf.gov/statistics

***Science* Careers How-To Guides**
sciencecareers.sciencemag.org/career_development/tools_resources/how_to_guides

Howard Hughes Medical Institute publications:

Making the Right Moves
www.hhmi.org/resources/labmanagement/mtrmoves_download.html

Training Scientists to Make the Right Moves
www.hhmi.org/resources/labmanagement/downloads/guide.pdf

Entering Mentoring
www.hhmi.org/resources/labmanagement/downloads/entering_mentoring.pdf

Teaching the Teacher

Teaching represents yet another obligation of a junior faculty member, and that teaching has to be balanced with research, lab management, and administrative duties. According to Mobley, it's important to understand from others what the best teaching styles are. "Try to convey your information as clearly and as simply as possible but engage your students—get students to help themselves learn, and give them opportunities to speak to you."

"Teaching and research are intimately intertwined," says Liotta. "If you're a good researcher and you don't know how to communicate those results, you're not going to be very effective." Liotta recommends using a camcorder to tape a few teaching sessions to identify and try to eliminate any idiosyncrasies. "Many people have habits that they don't realize and they're probably relatively easy to correct." He also points out that good notes and preparation can go a long way in producing a well-organized lecture in the beginning.

Playing Politics

The word "politics" carries many meanings, but in science, if politics means forming collaborations and generally getting along with people, then it plays a valuable role in advancing a career. But such politics cannot substitute for good science. "I certainly know some people who just spend their whole day on the telephone talking to everybody and finding out what everybody else is doing," Schwartz says. "It's far better to focus on doing, not just talking, science."

"In academic circles, good science, not politics, always wins," says Mobley. "Playing politics is potentially damaging. Focus on your scientific teaching, avoid politics in any way—only people who can't do science play that game," he adds.

Coyle agrees. "I've not been impressed that playing politics is the way to get ahead. I am impressed that if you really focus on your science, especially in the beginning of your career, and be very defensive about preserving your time to do your science, then that's probably the most important way of getting ahead academically," he says.

Love of Learning

While there may seem to be an overwhelming array of skills to master for tenure-track doctors of philosophy, "philosophy" does in fact mean "love of wisdom." And if there's one single defining characteristic among academics, it may be just that. Schwartz, therefore, advises approaching the mastery of these tasks as a lifelong learner, which makes it all more palatable.

"If you think about the job of a university faculty member, we're in a unique position," says Liotta. "We can do whatever kind of research we want to do and have the opportunity to work with bright young people year after year. We can go out and talk about our work with colleagues at meetings; we tend to have fairly flexible schedules so we can do a lot of interesting things, and you know—that's a fantastic job."

Emma Hitt is a freelance medical and science writer living in Marietta, Georgia.

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CHAIR
Pharmaceutical Sciences
University of Oklahoma College of Pharmacy

The University Of Oklahoma College Of Pharmacy invites applications and nominations for the position of **Chair, Pharmaceutical Sciences**.

The College of Pharmacy is located within the University of Oklahoma Health Sciences Center (OUHSC), a 325-acre comprehensive academic health center, recently noted for having one of the best academic institution work environments in the country by The Scientist (Nov, 2007). The Department of Pharmaceutical Sciences comprises the disciplines of pharmacology/toxicology, pharmaceutics, medicinal chemistry, immunology/infectious diseases, and nuclear pharmacy. At this time the department is undergoing a major expansion.

Departmental faculty members contribute to the Pharm.D., Ph.D. and Pharm.D./M.S. degree programs. Applicants must have a Ph.D. or equivalent degree and must demonstrate strong evidence of academic leadership and peer recognition as an accomplished researcher. The successful candidate is expected to have a strong track record of significant extramural research funding or industrial productivity. In addition, the candidate would have a strong commitment to professional and graduate education and the ability to recruit and develop outstanding faculty.

The Health Sciences Center has targeted growth in four broad areas: cancer, diabetes, neuroscience/vision, and immunology/infectious disease. The incoming Chair will have the opportunity to collaborate in those programs. The position provides open faculty lines, appropriate laboratory space, and an expanding graduate program. The successful applicant may also be eligible to receive one of several Endowed Professorships. Further information on the College of Pharmacy is available at: **http://pharmacy.ouhsc.edu/**.

OUHSC is situated in the capital city of Oklahoma City; an area experiencing economic growth and undergoing extensive revitalization. Oklahoma City is one of the most economically and geographically attractive major metropolitan areas in which to live.

Review of applications will begin **March 1, 2008** and continue until the position is filled. Candidates should send a letter describing research interests, administrative and educational philosophies and long-term goals, a curriculum vitae and the names, addresses (postal and email), phone and fax numbers of at least three professional references to: **Kevin Rinaldi, Attn: Pharmaceutical Sciences Chair Search Committee, College of Pharmacy, University of Oklahoma Health Sciences Center, PO Box 26901, Oklahoma City, OK 73126-0901; Phone: 405-271-6484, ext. 47291; E-mail: kevin-rinaldi@ouhsc.edu.**

The University of Oklahoma Health Sciences Center is an Equal Opportunity/ Affirmative Action Employer.

MAYO CLINIC

Mayo Clinic College of Medicine Faculty Position in Cancer Pharmacology

Under the auspices of the Minnesota Partnership for Biotechnology and Medical Genomics, the Division of Oncology Research and Department of Molecular Pharmacology and Experimental Therapeutics seek an outstanding, extramurally funded investigator in the area of cancer pharmacology. Applications at the level of Associate Professor or Professor are especially welcome. Individuals with expertise in proliferative signaling, cell cycle checkpoints, DNA repair, cancer pharmacogenomics and/or rational drug design are particularly encouraged to apply. Research in the Division is described at **http://mayoresearch.mayo.edu/mayo/research/developmental_therapeutics/**.

A *curriculum vitae*, selected publications, and a statement of research interests, should be submitted to: **Deb Strauss (strauss.debra@mayo.edu) or to Scott Kaufmann, M.D., Ph.D., Guggenheim 1301, Mayo Clinic, Rochester, MN 55905** by **April 30, 2008**.

The Mayo Clinic College of Medicine is an Equal Opportunity Educator and Employer.

ASSISTANT/ASSOCIATE MEDICAL PROFESSOR IN PHARMACOLOGY

the City College of New York

Location/Department: Department of Physiology & Pharmacology
FLSA Status: Exempt
Compensation: $80,000 - $90,000
College Web Site: www.ccny.cuny.edu
Notice Number: FY - 13459
Closing Date: Open until filled.

POSITION DESCRIPTION AND DUTIES

The CUNY Medical School seeks an Assistant/Associate Medical Professor in Pharmacology in the Department of Physiology and Pharmacology. Applicants should be qualified to teach basic principles of Pharmacology to medical students.

QUALIFICATION REQUIREMENTS

Ph.D. and/or M.D. with two (2) years of postdoctoral work in any area of Pharmacology. Candidates must have demonstrated a strong record of scholarly research and publications in Pharmacology. Preference will be given to candidates with funded research programs who employ cellular, molecular, biochemical or behavioral research approaches.

The City College of New York has a strong institutional commitment to the principle of diversity. In that spirit, we are particularly interested in receiving applications from a broad spectrum of individuals, including women and under-represented groups. Upon request, reasonable accommodations provided for individuals with disabilities.

All candidates must provide documentation to prove employment eligibility in compliance with IRCA.

TO APPLY

Please submit a current curriculum vitae, statement of research plan and names and contact information of three(3) references to: **The Pharmacology Search Committee PVN # FY - 13459, Department of Physiology & Pharmacology, The CUNY Medical School/Sophie Davis of Biomedical Education, The City College of New York, 160 Convent Avenue, HR 203, New York, NY 10031.**

The City University of New York is an Equal Employment Opportunity/Affirmative Action/Immigration Reform and Control Act/Americans with Disabilities Act Employer

CITY COLLEGE IS CUNY

PVLSI PIONEER VALLEY LIFE SCIENCES INSTITUTE

TWO NEW FACULTY POSITIONS

METABOLIC REGULATION/DIABETES

The Pioneer Valley Life Sciences Institute (**www.PVLSI.org**) is seeking a new **Faculty member (rank open)** who studies metabolic regulation and/or diabetes to join a collaborative research program of basic and clinical researchers.

APOPTOSIS

The Pioneer Valley Life Sciences Institute (**www.PVLSI.org**) and the new Center of Excellence in Apoptosis Research are seeking a new **Faculty member (rank open)** who studies apoptosis with a focus on either disease or the development of new technologies.

We welcome a variety of experimental approaches including: physiology, genetics and molecular biology. Expertise in mitochondria, cell death or thermoregulation particularly welcomed.

Successful candidates will have an M.D. and/or Ph.D., post-doctoral experience, and depending on rank, a record of developing and maintaining an extramurally funded research program. Practicing physicians are encouraged to apply and can seek a clinical appointment in the appropriate department at the Baystate Medical Center, the western campus of Tufts University School of Medicine.

The PVLSI is an independent non-profit research organization that is jointly operated by the Baystate Medical Center (**www.Baystatehealth.com**) and the University of Massachusetts Amherst (**www.UMass.edu**). Researchers will have the opportunity to work closely with physicians and basic scientists in a newly built and well-equipped facility. Applicants should submit CV, statement of research plans, and three letters of reference to: **Dr. Lawrence Schwartz, PVLSI, 3601 Main Street Springfield, MA 01199** or via e-mail to **Lawrence.Schwartz@bhs.org** (PDF format preferred).

The PVLSI is an Equal Opportunity/Affirmative Action Employer.

University of Glasgow

Department of Physics and Astronomy

Professor of Physics in Solid State Physics

A Professorial appointment is available for a candidate who will provide scientific leadership in the Solid State Physics group, and conduct world class research on aspects of materials physics, preferably involving the development and use of electron and ion beam microscopy and analysis. The candidate will also play a key role, with colleagues, in developing and implementing departmental strategy in research and teaching.

Should a candidate of appropriate stature and reputation present themselves, they will be appointed to the Chair of Natural Philosophy at the University.

For further information on the post please contact Professor Robin Leake, Pro-vice Principal, email R.Leake@admin.gla.ac.uk quoting Ref: 13969/HRO/A1.

To find out more, and to apply, go to physics-at-glasgow.co.uk

Closing date: 14 March 2008.

The University is committed to equality of opportunity in employment.

www.glasgow.ac.uk Scottish University of the Year

Weill Cornell Medical College in Qatar

BIOLOGIST

FACULTY POSITION

WCMC-Q seeks candidates for a faculty position with major responsibility for the teaching of an introductory biology sequence of two courses in a premedical program leading to entry to the medical school. Another faculty member conducts a complementary laboratory course sequence. Beyond the principal teaching obligation a successful applicant is expected to participate in advising, committee work, and the academic life of WCMC-Q. Research space is available as well as research funding support. Details regarding the WCMC-Q program and facilities can be accessed at:

www.qatar-med.cornell.edu

Candidates should hold a Ph.D. degree and possess demonstrable teaching skills as well as experience and training in research. Candidates must be willing to relocate to Doha, Qatar for the duration of the appointment. Academic rank and salary are commensurate with training and experience and are accompanied by a competitive foreign-service benefits package. Qualified applicants should submit a curriculum vitae and a letter of interest outlining their teaching and research experience to:

facultyrecruit@qatar-med.cornell.edu

***Please quote Faculty Search #08-sci-B01 on all correspondence**

Cornell University is an equal opportunity, affirmative action educator and employer.

The screening of applications will begin immediately and continue until suitable candidates are identified. Service is expected to begin in August 2008.

Please note, short-listed candidates will be asked to provide names of three references.

DIRECTOR

Regional Biocontainment Laboratory

The UMDNJ-New Jersey Medical School invites applications for the position of Director of the new Regional Biocontainment Laboratory (RBL). The position will be supported by substantial institutional resources including outstanding laboratory facilities within the newly constructed 35,000 sq. ft RBL, which is scheduled to open in Spring 2008. We seek a senior scientist with a strong record of research accomplishments working with category A-C biodefense and/or emerging infectious disease pathogens. The Director is expected to establish a robust core research program and recruit investigators capable of attracting NIH funding. Successful candidate will also play a pivotal role in expanding strategic research and translational partnerships with academia, biotech and pharma. This is an exciting opportunity to join a growing and highly interactive infectious diseases research network in Newark, including the Departments of Medicine and Microbiology and Molecular Genetics, the Public Health Research Institute, the Center for Emerging Pathogens, the Center for Immunity and inflammation, and the Northeast Biodefense Center. Current research interests focus on bacterial and viral pathogenesis, diagnostic development, immunology, innovative vaccine and therapeutic strategies, molecular epidemiology, and bioinformatics. The new RBL adds to an existing infrastructure of BSL-3 and ABSL-3 containment facilities, which is one of the most extensive in the Northeast.

FACULTY POSITION

Microbial Pathogenesis

Applications are invited for tenure/tenure-track faculty positions in microbial pathogenesis, with rank commensurate with qualifications. Applicants with an interest in biodefense and emerging infectious diseases pathogens, and expertise in host-pathogen interactions are particularly encouraged to apply. The successful candidate will have demonstrated research productivity and will be expected to maintain an independent, innovative, funded research program and to participate in graduate and postgraduate training. A competitive start-up package and outstanding core facilities are available, including animal imaging, informatics, and extensive BSL-3 and ABSL-3 containment facilities.

Applicants should submit a curriculum vitae, a statement of research experience, a summary of future plans, and names of three references by February 29, 2008, to: **Dr. Nancy Connell, e-mail: connell@umdnj.edu.** AA/EEO Employer M/F/D/V.

UMDNJ

NEW JERSEY MEDICAL SCHOOL

University of Medicine & Dentistry of New Jersey

UNIVERSITY OF MISSOURI-COLUMBIA

Tenure Track Position in Nutrition and Food Science

The University of Missouri invites applications for a nine-month, tenure track faculty position in the newly expanded Nutritional Sciences Department that now spans three colleges: Medicine, Agriculture, and Human Environmental Sciences. The successful candidate will help fulfill a new Department mission focused on an interdisciplinary approach to investigating the obesity epidemic spanning from pipette to patient to population to policy. This position is part of an ongoing effort at MU to hire six new faculty in Nutritional Sciences and is funded through the Food for the 21st Century Nutritional Sciences Cluster, an interdisciplinary group built on a strong tradition of interaction between medical, biological and agricultural sciences on this campus. Of particular interest are candidates with strength in one or more of the following areas:

- Food-based obesity interventions
- Nutritional interventions using functional foods
- Microbial-host interactions in obesity

Recruitment will be at either the Assistant or Associate Professor level. Applicants must have a doctoral degree, postdoctoral experience, and evidence of outstanding research potential. It is expected that the successful candidates will participate in the core functions of the Nutritional Sciences Department, establish an internationally recognized research program via both independent and interdisciplinary collaborations, train graduate students, and contribute to the undergraduate instructional program. Successful candidates will be provided with excellent laboratory space, generous start-up funds, along with a supplemental annual operating budget of $50,000 per year for a minimum of five years. Starting salary will be competitive and commensurate with experience. Columbia has the residential advantages of a major university town: excellent schools, and many recreational and cultural opportunities, as well as easy access to St. Louis and Kansas City. Information about the departments of Nutritional Sciences and Food Sciences can be found at the departmental links (**http://ns.missouri.edu and http://foodscience.missouri.edu, respectively**). Questions and applications can be directed to: **Dr. Kevin Fritsche, Chair of the Search Committee at FritscheK@missouri.edu**. An application must include curriculum vitae with a complete list of publications, a concise summary of research interests and future plans, and the names of four individuals prepared to write letters of recommendation. To ensure full consideration, applications should be received by April 15, 2008.

The University of Missouri is an Affirmative Action, Equal Opportunity employer.

Visit the University of Missouri-Columbia's web site at http://mujobs.missouri.edu

West Virginia University
ROBERT C. BYRD HEALTH SCIENCES CENTER

RESEARCH POSITIONS

Positions available at the rank of **Research Assistant Professor, Research Instructor** and **Post-Doctoral Fellow** for **NIH and VA funded laboratory** to study mechanisms responsible for myocardial dysfunction in a variety of cardiomyopathy models using a combination of cutting-edge and classic techniques at the in vivo, organ, tissue, cellular and molecular levels. This laboratory is part of the new **CENTER FOR INTERDISCIPLINARY RESEARCH IN CARDIOVASCULAR SCIENCES (CIRCS) at WEST VIRGINIA UNIVERSITY SCHOOL OF MEDICINE**.

The positions will remain open until filled. Interested applicants with relevant training and experience should submit a copy of their curriculum vitae and three references to:

Mitchell S. Finkel, M.D.
West Virginia University
School of Medicine
Departments of Medicine (Cardiology)
PO Box 9157
Morgantown, WV 26506-9157
cardresearch@hsc.wvu.edu

WVU is an Equal Opportunity/Affirmative Action Employer. Women and Minorities are encouraged to apply.

ASSOCIATE DEAN
Graduate School of Biomedical Sciences

The University of Medicine and Dentistry of New Jersey-New Jersey Medical School and the UMDNJ-Graduate School of Biomedical Sciences (GSBS) invite nominations and applications for the position of Associate Dean for GSBS at New Jersey Medical School. Responsibilities will include leadership and management of the newly restructured Graduate School of Biomedical Sciences at New Jersey Medical School on the UMDNJ Newark campus. The ideal candidate will possess a Ph.D. degree, or the equivalent, and a strong record of funded research and publications, student mentoring and administration. The successful candidate should be eligible for a senior-level appointment in an appropriate department.

The Graduate School of Biomedical Sciences at New Jersey Medical School is well established and offers programs leading to MS, MBS, MS/MBA, Ph.D., and M.D./Ph.D. degrees, with Ph.D. programs in Biochemistry & Molecular Biology, Biomedical Engineering (with New Jersey Institute of Technology), Biomedical Sciences (Interdisciplinary), Cell Biology & Molecular Medicine, Microbiology & Molecular Genetics, Molecular Pathology & Immunology, Neuroscience (with Rutgers University), and Pharmacology & Physiology.

For further information or to apply, please e-mail your curriculum vitae and a cover letter, explaining your interest in and qualifications for the position, to: **gsbsnsearch@umdnj.edu.** Electronic submission of CVs in PDF format is strongly encouraged. If electronic submission is not possible, please mail your CV to: **Michael Petti, Executive Assistant to the Dean, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, MSB C671, Newark, New Jersey 07101-1709.** AA/EEO Employer M/F/D/V.

UMDNJ
NEW JERSEY MEDICAL SCHOOL
University of Medicine & Dentistry of New Jersey

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Faculty Positions

The Weizmann Institute of Science invites applications for tenure-track positions at the level of assistant professor, associate professor or professor in the natural and exact sciences.

We are looking for applicants with a PhD and a record of outstanding accomplishment who possess the ability to lead an independent research group. Those applying should be prepared to make major contributions to the advancement of science and have the potential to become future international leaders in their fields. Selection will be based on originality, independence, achievement and the likelihood that the applicant will be further promoted in the near future.

The submission deadline for applications is April 30th, 2008.

Please send 3 copies of your application letter, which should include a statement of current and future research interests (up to 3 pages) and your curriculum vitae, to the Academic Secretary, Weizmann Institute of Science, P.O.B. 26, Rehovot 76100, ISRAEL

For further details see: **http://www.weizmann.ac.il/acadaff/academic_positions.html**

FACULTY POSITION IN NEUROSCIENCE
Montreal Neurological Institute of McGill University

The Montreal Neurological Institute (MNI) is expanding our program in neuronal development and disease. We seek an individual whose research addresses fundamental issues of neuronal biology, including transcriptional control of neural development, functional and structural properties of neurons, organization of neural circuits, mechanisms for neuronal survival, and/or the underlying biology of neural disease including motor control. Outstanding candidates in all fields of neuroscience will be considered, but those using molecular, electrophysiological and genetic approaches are especially encouraged to apply.

The ideal candidate is a creative, accomplished scientist with an established, internationally recognized research program. An endowed chair has been committed to this effort and individuals at mid-career levels are especially encouraged to apply.

The MNI (www.mni.mcgill.ca) houses 58 independent research labs that cover the full range of neuroscience from molecular biology to systems and cognitive neuroscience. These activities include a state of the art brain imaging centre for both human and animal studies. The neuroscience communities of McGill and greater Montreal are among the largest and most diverse in North America. In addition, the MNI is adjacent to research centres dedicated to proteomics, genomics, and bioinformatics. We offer highly attractive salary and start-up packages and an exceedingly high quality of life in Montreal, one of North America's greatest and most lively cities.

Applications should consist of a letter outlining your research interests, a copy of your CV, and the names and addresses of three references.

Chair, Search Committee
Room 636, Montreal Neurological Institute
McGill University
3801 University Street
Montreal, Quebec H3A 2B4, Canada

Send email inquires and applications to:
facultysearch.mni@mcgill.ca
Application deadline: March 31, 2008

McGill University is committed to equity in employment and diversity. It welcomes applications from indigenous peoples, visible minorities, ethnic minorities, persons with disabilities, women, persons of minority sexual orientations and gender identities and others who may contribute to further diversification. All qualified applicants are encouraged to apply; however, in accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada.

Faculty Position
Institute of Biomedical Sciences
National Sun Yat-Sen University

The Institute of Biomedical Sciences, National Sun Yat-Sen University is seeking for outstanding scientists for a tenure-track faculty position (assistant/associate/full professor). Successful candidates must hold a Ph.D. or M.D./Ph.D. degree in Biomedical Science related discipline with a significant record of publication and graduate/postdoctoral training.

Faculty members are expected to establish a highly visible externally funded research program, to excel in teaching graduate (master and Ph.D.) students and to serve public affairs of the institute. An attractive startup package including basic laboratory facilities and start funds will be available.

Candidates should submit the following issues (1) certification documents for education, training and other important experiences (2) curriculum vitae including a publication list and paper reprints in the past five years (3) three letters of recommendation (4) a statement of future research goals and teaching interests. Written applications should be sent to: **Prof. Wen-Chun Hung, Institute of Biomedical Sciences, National Sun Yat-Sen University, No. 70, Lien-Hai Road, Kaohsiung 804, Taiwan, Republic of China**. Inquiries regarding the position may be e-mailed to Prof. Wen-Chun Hung and the deadline for application is **February 29, 2008**. Potential candidates will be notified and interviewed by the search committee of the institute.

The University of Georgia

Physical and Microbial Oceanography

The Department of Marine Sciences of the University of Georgia's School of Marine Programs seeks two tenure-track Assistant Professors for Fall 2008.

Physical Oceanographer - We seek candidates having interests in global, regional and/or coastal physical oceanographic processes with expertise in modeling and/or observational analysis. Specific areas of interest include, but are not limited to, air/sea interactions, nearshore processes including extreme forcing, buoyancy transport, deep-ocean mixing processes, turbulent fluid dynamics and large-scale phenomena contributing to climate change.

Microbial Oceanographer - We seek candidates having interests in bacterial, archaeal, or single-celled eukaryote ecology. Potential areas of interest include microbial processes related to biogeochemical cycling or global climate change, metagenomics, and biosensor development, but other areas will be considered.

Current faculty conduct research on a wide range of biological, chemical and physical processes in marine and freshwater environments and collaborate on large-scale studies at the land/sea interface. The successful candidate will be expected to develop an independent, funded research program and to participate in graduate and undergraduate instruction. The candidate will be encouraged to collaborate with faculty in the School of Marine Programs in Athens, the Marine Institute on Sapelo Island, the Marine Extension Service, and other University System of Georgia programs. Please visit the Department's web page at **www.marsci.uga.edu** for additional information. Specific inquiries may be addressed to: **Dr. Daniela Di Iorio** for physical oceanography or **Dr. Mary Ann Moran** for microbial oceanography at **marsdir.uga.edu**.

Applicants should send a curriculum vitae, brief statement of research and teaching interests, and names and addresses of three references to: **Chair, Search Committee, Department of Marine Sciences, 211 Marine Sciences Building, University of Georgia, Athens GA 30602-3636**. Applications can be submitted electronically to **marsdir@uga.edu**. Review of applications will begin **March 15, 2008**. Applications received by that date are assured consideration.

The Franklin College of Arts and Sciences, its many units, and the University of Georgia are committed to increasing the diversity of its faculty and students, and sustaining a work and learning environment that is inclusive. The University is an EEO/AA Institution.

Tufts

Tufts University School of Medicine
Faculty Positions in Neuroscience

The Department of Neuroscience **www.neurosci.tufts.edu/indexDept.html** at Tufts University School of Medicine is expanding by adding nine tenure-track faculty positions. Positions are available at Assistant, Associate and Full Professor levels. The department will build on its core strengths and focus on the study of synapses, disorders of the nervous system and neuron-glial interactions. We are seeking candidates who use innovative approaches to investigate problems that cross levels of investigation from molecular and cellular to systems and/or behavioral neuroscience. Candidates using molecular, genetic, electrophysiological and/or imaging methodologies to study neurons, synapses and networks are particularly encouraged to apply. We offer generous start-up packages, newly renovated laboratory space and a highly collaborative environment offering opportunities for both basic and translational research.

Applicants should hold a Ph.D. and/or M.D. degree and have several years of productive postdoctoral experience. Successful candidates will be expected to develop thriving, well-funded research programs and to contribute to graduate and medical education. Please submit electronic applications including a CV, a statement of research interests and the names and email addresses of at least three references to: **neurosci-facultyrecruitment@tufts.edu**.

TUSM is an Equal Opportunity Affirmative Action Employer. Women and minorities are encouraged to apply.

FACULTY POSITION
Assistant Professor
Genetics, Stem Cell or Systems Biology

Brigham and Women's Hospital
Harvard Medical School

The Genetics Division, Department of Medicine at Brigham and Women's Hospital and Harvard Medical School, seeks an outstanding Assistant Professor level scientist. Applicants should possess Ph.D., M.D., or M.D., Ph.D. degrees and have several years of relevant postdoctoral experience. Areas of interest are broad; these include human genetics, model organism genetics, systems level analyses of pathways involved in disease and development, stem cells, tissue and organ regeneration, and proteomics. The successful applicant will enjoy an outstanding competitive start-up package, excellent space and state-of-the-art facilities, and will be part of a division with diverse interests and expertise: **http://brighamandwomens.org/research/Genetics/**.

Please send by **April 15, 2008** a CV, a 2-3 page description of research interests and plans, and 3 letters of recommendation to:

David Beier, M.D., Ph.D.
Chair, Search Committee
c/o Suzanne Peterson
BWH Genetics Division
New Research Bldg., NRB 458D
Harvard Medical School
77 Avenue Louis Pasteur
Boston, MA 02115

Electronic submissions are preferred:
SPETERSON5@PARTNERS.ORG

BWH is an Equal Opportunity Employer.

ASSOCIATE or FULL PROFESSORS

The Department of Cell Biology at Duke University invites applications for tenured positions at the Associate or Full Professor level. We are particularly interested in candidates investigating a biological process or question relevant to human health and disease from the molecular through to the organismal level. Candidates working on stem cell biology are also encouraged to apply. A strong track record of scholarly achievement, innovation, and collaboration is a priority. Successful candidates will enjoy newly renovated space and a highly collegial and interactive environment. Learn more at: www.cellbio.duke.edu

Candidates should submit CV, statement of current and future research plans, and names of three professional references to: **Dr. Brigid LM Hogan, Chair, Department of Cell Biology, Room 388C, Nanaline H. Duke Building, Box 3709, Duke University Medical Center, Durham, NC 27710**. Position is open until filled.

DUKE UNIVERSITY

Duke University is an Equal Opportunity/Affirmative Action Employer.

Faculty Position
UNMC Eppley Institute for Research in Cancer and Allied Diseases

The **Eppley Institute for Research in Cancer and Allied Diseases**, a multi-disciplinary cancer research institute at the **University of Nebraska Medical Center (UNMC)**, invites applications for tenure-leading positions at all levels. We seek candidates with outstanding records of cancer research achievement focusing on basic molecular and cellular mechanisms, molecular therapeutics, or specific disease models. Researchers with expertise using chemical genetic or chemical genomic approaches, including, but not limited to state-of-the-art techniques for identifying small molecules directed at cancer targets, *in vitro* and *in vivo* methods to enhance molecular target validation, and techniques for identifying and validating cancer biomarkers are encouraged to apply.

The Eppley Institute for Research in Cancer and Allied Diseases, an integral part of both the University of Nebraska Medical Center and the UNMC Cancer Center (NCI-designated Cancer Center), continues aggressive recruitment of outstanding scientists in several areas of scientific priority. The Institute provides a supportive environment that fosters creative, multidisciplinary research with world-class laboratory facilities, state of the art core facilities, and outstanding institutional and state support. New faculty will find a collaborative scientific environment coupled with very competitive start-up packages. Both pre- and post-doctoral fellowships are available for support of trainees. Omaha, the nation's 42nd largest city, offers an outstanding school system, low cost of living, and numerous recreational activities.

Candidates should have a Ph.D. and/or M.D. degree and postdoctoral research experience. Applicants can apply online to position **#2468** at **https://jobs.unmc.edu**. Additional information can be found at **http://www.unmc.edu/cancercenter/**. Candidates should also forward a minimum of 3 letters of reference to: **Search Committee, Eppley Institute for Research in Cancer and Allied Diseases, Attn: Matt Winfrey, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, Nebraska, 68198-6805.**

The University of Nebraska Medical Center is an Equal Opportunity Employer.

Faculty position
Molecular Cardiovascular Biology

The Division of Molecular Cardiovascular Biology at Cincinnati Children's Hospital Medical Center is initiating a search for a **tenure track** position at the **Assistant, Associate or full Professor** level. The successful candidate will have a PhD, MD or MD-PhD degree and at least two years of post-doctoral research experience. The Division occupies outstanding new research space in a state-of-the art, 450,000 ft^2 building that opened in December, 2007.

Division faculty may join the multi disciplinary graduate program in Molecular and Developmental Biology. The applicant will have a demonstrated track record in one or more of the following areas: molecular aspects of cardiogenesis, normal or abnormal heart development and function, the genetic basis of cardiovascular disease, cardiac signaling, molecular approaches to cardiac physiology, gene regulation, or the application of global approaches to the cardiovascular system.

The successful applicant will be joining a highly productive and interactive faculty. Ample laboratory space in the new building and a generous multi-year start-up package will be provided. Applications should include a comprehensive curriculum vita, the names of three references, a summary of past research and future research plans. Applications should be emailed to: **Jeff.Robbins@cchmc.org**

Cincinnati Children's Hospital Medical Center

Visit our website at www.cincinnatichildrens.org

Cincinnati Children's Hospital Medical Center is an Affirmative Action/Equal Opportunity Institution. Women and minorities are encouraged to apply.

Faculty positions for cardiovascular molecular medicine in Peking University, China

The Institute of Molecular Medicine at Peking University is inviting applications for three Principal Investigator Positions, at the rank of (equiv. to U.S.) asst., assoc. or full professor. Successful applicants are expected to head research and education programs in vascular biology; nonhuman primate models of cardiovascular and metabolic diseases; and cardiac development and regenerative medicine, respectively. Competitive startup packages with benefits will be provided. Interested applicants with demonstrated academic excellence and leadership in respective fields should submit CV and statement of research interest to Dr. Heping(Peace) Cheng at imm@pku.edu.cn. Inquiry phone/fax: +86-10-6276-7143; web: http://www.pku.cn:8000/academic/imm/.

University of California, Davis Department of Pharmacology Faculty Positions in Pharmacology

The University of California, Davis, School of Medicine, Department of Pharmacology invites applications for two - four (2-4) full-time academic tenure track position(s) at the Assistant/Associate/Full Professor level. **http://www.ucdmc.ucdavis.edu/pharmacology/**.

The Pharmacology Department is housed in the new UC Davis Genome Center and recently successfully recruited a new Department Chair, **Dr. Donald M. Bers, Ph.D.**, with plans for significant growth, including recruitment of up to 5 new faculty in the coming 3 years. One area of anticipated research growth within the department is cardiovascular, but candidates with strong research programs in other areas are welcome. Pharmacology has strong links to the Genome Center, Center for Neuroscience, Physiology and Membrane Biology, UC Davis Health System Cancer Center and Cardiovascular research groups.

Candidates must possess a Ph.D. and/or M.D. degree and at least two years of productive postdoctoral experience. Individuals selected for the position(s) will be expected to build or continue a successful, independent, extramurally funded research program and to achieve excellence in the teaching of basic sciences to medical and graduate students. The most important criteria in the consideration of applications are: (1) a record of excellence, creativity, and initiative in research, which establishes a strong potential to build a vigorous and competitive research program; and (2) a demonstrated ability to communicate effectively as a teacher participating in the teaching of medical and graduate students. Research areas should complement others in Pharmacology and campus programs. Particular interests include function, expression, trafficking, signaling pathways, structure and regulation of membrane proteins (such as ion channels and receptors) and novel therapeutic strategies. Priority will be given to candidates whose record of innovative research and commitment to teaching demonstrate their potential as leaders in their fields.

These positions will be open until filled, but for full consideration applications should be received by **March 1, 2008**. Applicants should send a curriculum vitae, up to three key reprints, a synopsis of research interests and plans (past, present and future goals), a summary of teaching experience/philosophy and the names/addresses of three to five references to be sent to: **Peter M. Cala, Ph.D., Interim Chair, Department of Pharmacology, attention: Tom Watkins, Genome Building, Room 3502, 451 Health Sciences Drive, UC Davis, Davis, CA, 95616**. Search #s **PH-06R-08**.

The University of California is an Affirmative Action/Equal Opportunity Employer.

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Neuroscience Faculty Recruitment

The Department of Neuroscience at Columbia University Medical Center, as part of a University-wide Neuroscience Initiative, is recruiting faculty concentrating on the analysis of neural circuitry through molecular, genetic, cellular electrophysiological and/or imaging approaches. We are particularly interested in individuals whose research program explores neural circuits in genetically tractable model systems and in the context of well-defined behaviors. We encourage applications for positions at the Assistant Professor level but will also consider applications from more senior investigators for positions at the level of Associate or Full Professor.

Columbia University currently has a world-renowned program in neurobiology and behavior and the Neuroscience Initiative aims to enhance interactions between basic and clinical neurosciences and link the neurosciences to other scientific disciplines within the University. Faculty will be affiliated with the Department of Neuroscience, and there will be opportunities for strong ties with scientific departments and programs on the Morningside Heights campus.

Applications for this round of recruitment are requested by March 1, 2008. A CV, cover letter, including statement of interests, and three letters of reference under separate cover should be e-mailed care of David Leyden, dgl2102@columbia.edu. In addition, please mail a hard copy of these documents to:

Chair, Neuroscience Search Committee
c/o: David Leyden
Columbia University
Hammer Health Sciences Center
Room 2-205G
701 W 168th Street
New York NY 10032

Columbia University takes affirmative action to ensure equal employment opportunity.

UNIVERSITY *of* CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE

UCSD Medical Genetics Division Director - The Department of Medicine at the UCSD School of Medicine in conjunction with the UCSD Center for Human Genetics and Genomics invites applications for a Chief of the Division of Medical Genetics from outstanding individuals, to develop a vigorous research program in any area of contemporary human genetics and genomics. The appointment will be full time at the Associate or Full Professor level, and will involve teaching at both the graduate and medical school levels. Candidates must possess a M.D. or Ph.D. degree and be trained in any area of contemporary Human Genetics and Genomics with a demonstrated track record of outstanding peer-reviewed research. Board certification in any area of Medical Genetics is desirable but not essential. Research space will be provided in the Center for Human Genetics and Genomics on the 4th floor of the new Skaggs School of Pharmacy and Pharmaceutical Sciences building or other sites within the UCSD Health Sciences campus. In addition, an attractive and competitive start-up package will be provided. The goal of the center is to galvanize already existing genetics and genomics efforts throughout the School of Medicine and UCSD campus, and coordinate efforts within the Department of Medicine to advance our biomedical sciences. Rank and series of appointment will be commensurate with the candidate's skills, qualifications and experience. Salary will be based on published UC pay scales.

Applicants should e-mail their curriculum vitae and names and addresses of three references to **doconnor@ucsd.edu** or mail to: **Daniel T. O'Connor, M.D., Professor of Medicine and Chair, Division of Medical Genetics Chief Search Committee, University of California, San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0838.** Review of applications will begin on **March 21, 2008** and will continue until the position is filled.

UCSD is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity.

UBC OKANAGAN

THE UNIVERSITY OF BRITISH COLUMBIA OKANAGAN

British Columbia Regional Innovation Chair in Reservoir Ecosystem Management

The University of British Columbia (UBC) is ranked among the world's 40 best universities and its newest campus is located in the heart of the scenic Okanagan Valley. The Irving K. Barber School of Arts and Sciences, the largest Faculty at UBC Okanagan, seeks an outstanding scholar who will lead in the development and integration of interdisciplinary, innovative, science-based approaches to best-management of reservoirs. Applications from those having demonstrated expertise in applied aquatic ecosystem ecology, bio-geomorphology of littoral zones in reservoirs or impacts of reservoir management on lacustrine and fluvial systems are particularly encouraged.

The successful candidate will have a PhD with a strong research record, exceptional communication skills, demonstrated excellence in teaching at both the undergraduate and graduate levels, and a background of working effectively with stakeholders on applied problems. The position is contingent on funding and will be affiliated with one or more of the programs within the Irving K. Barber School of Arts and Sciences.

The University of British Columbia Okanagan hires on the basis of merit and is committed to employment equity. We encourage all qualified persons to apply; however, Canadians and permanent residents of Canada will be given priority.

For more information please visit our website:
http://web.ubc.ca/okanagan/ikbarberschool/employment.html

University at Buffalo
The State University of New York

Faculty Position in Pharmaceutical Sciences

Department of Pharmaceutical Sciences
School of Pharmacy and Pharmaceutical Sciences
Faculty of Health Sciences
(http://pharmsci.buffalo.edu)

Applications are invited for a tenure-track position, which will be filled at the level of Assistant or Associate Professor.

We seek applicants with a demonstrated record of research excellence and a focus upon the discovery and development of protein therapeutics. Areas of interest include protein engineering, delivery approaches, the evaluation of protein therapeutics in animal models of disease, and in translational research.

A PhD in a relevant field is necessary and post-doctoral experience is highly desirable.

The successful candidate is expected to develop an independent and extramurally funded research program, to participate within the UB Protein Therapeutics Consortium at the University at Buffalo, and to participate in undergraduate and graduate instruction.

An applicant should submit an on-line application, letter of intent, curriculum vitae, the names and addresses of three references, and a statement of research interests at: **www.ubjobs.buffalo.edu**; Posting Number **#0601951**. For additional position information, please contact: **Sathy Balu-Iyer, PhD, Search Committee Chair, School of Pharmacy and Pharmaceutical Sciences, 521 Hochstetter Hall, University at Buffalo, Buffalo, New York 14260-1200.** Telephone: 716-645-2842, ext. 229, FAX: 716-645-3693, email: **svb@buffalo.edu.**

The University at Buffalo is an Equal Opportunity/Affirmative Action Employer/Recruiter.

Assistant Professor of Tree Fruit Genomics - #08011

Cornell University is a bold, innovative, inclusive and dynamic teaching and research university where staff, faculty, and students alike are challenged to make an enduring contribution to the betterment of humanity.

The Department of Horticultural Sciences and New Life Sciences at Cornell University seeks an assistant professor in tree fruit genomics. This position creates a unique opportunity for a scholar to develop a tree fruit genomics program at an institute with an extensive portfolio of tree fruit research and extension. The Cornell New Life Sciences Initiative coupled with extensive expertise in tree fruit breeding, physiology, and management, and access to a rich collection of genetic resources create a vibrant intellectual environment for study of tree fruit genomics. The appointee will work with a University-wide team using genomic approaches and, as appropriate, the latest techniques in biochemistry, genetics, analytical chemistry, and molecular and cell biology.

Tenure track; 70% Research, 30% Extension. Nine-month academic-year appointment basis. ***Starting date:*** August 1, 2008 or as negotiated. ***Responsibilities:*** The ideal appointee will be a geneticist or a molecular biologist with expertise in functional genomics. Research will involve discovery and characterization of apple genetic resources. Examples of appropriate research include, but are not limited to, plant growth and development, including plant architecture, plant reaction to biotic and abiotic stress, and fruit quality. The extension program will be focused on educating several constituencies about the capabilities and benefits of genomics research for fruit production and management. Constituencies will include farmers, production specialists, governmental officials and policy advisors.

Qualifications: Ph.D. in plant genomics, plant molecular genetics, molecular biology or closely related area in plant science. A demonstrated record of excellence in genomics as evidenced by publication in peer-reviewed journals is desired. Preferred qualifications include postdoctoral experience, commitment to (and abilities in) team research, ability to communicate effectively with students, colleagues and external stakeholders.

Salary: Competitive, commensurate with background and experience. An attractive fringe benefits package is available.

Application procedure: Send a letter of application, curriculum vitae, selected reprints, academic transcripts, statement of research goals and plans, and names and addresses of three references to:

Dr. Susan Brown, Search Committee Chair
Department of Horticultural Sciences
630 W. North Street, NYSAES
Cornell University, Geneva, NY 14456
E-mail: skb3@cornell.edu
Phone: 315-787-2224 Fax: 315-787-2216

The Department actively encourages applications from women and minority candidates. Review of applications will begin March 1, 2008 and will continue until the position is filled. ***Department Affiliation:*** The successful candidate will be a faculty member of the Cornell University College of Agriculture and Life Sciences, and will be based in the Department of Horticultural Sciences at the New York State Agricultural Experiment Station (NYSAES) in Geneva, NY (**http://www.nysaes.cornell.edu/hort/**). A mentoring program for new faculty provides guidance and assistance.

Cornell University
Cornell University is an Affirmative Action/ Equal Opportunity Employer and Educator.

http://chronicle.com/jobs/profiles/2377.htm

Faculty Position in Bacteriology

The Department of Molecular Microbiology and Immunology at the Oregon Health & Science University invites applications for a tenure-track position at the Assistant or Associate Professor level. Applicants should possess a Ph.D. and/or M.D. degree with postdoctoral experience with a significant record of publication on prokaryotic microorganisms. All areas of prokaryotic microbiology will be considered, but those related to pathogenic bacteria are of special interest. The successful candidate will be expected to develop a vigorous program of research and to participate in teaching of graduate and medical students. OHSU places high priority on cultural diversity; thus, we seek candidates with demonstrated sensitivity to and understanding of the diverse academic, socioeconomic, cultural, disabled and ethnic backgrounds of OHSU's students and employees.

Applications should contain a current C.V., a 1-2 page statement of research program, and names, addresses, and E-mail contacts for 3 references. Material should be submitted electronically to **Kathy Shinall**, Search Committee Coordinator at **shinallk@ohsu.edu**.

OHSU is an Affirmative Action, Equal Opportunity Employer. Women, minorities, disabled persons, Vietnam era and disabled veterans are encouraged to apply. OHSU is a smoke free workplace.

The Cluster of Excellence *'Engineering of Advanced Materials – Hierarchical Structure Formation of Functional Devices'* (eam.uni-erlangen.de) at the Friedrich-Alexander-University of Erlangen-Nuremberg, Germany (FAU), and funded by the Deutsche Forschungsgemeinschaft (DFG) invites applications for a permanent

W3-Professorship in 'Multiscale Simulation of Particulate Systems'

Successful candidates should provide outstanding research leadership in the area of multiscale modeling and simulation in the context of mesoscopic materials science, granular physics, multiphase flow, dissipative particle dynamics, discrete elements or dynamic density functional theory. The successful candidate is expected to be experienced in interdisciplinary and externally funded research and to develop an internationally recognized fundamental research program strongly interlinked with the cluster's research areas, thereby bridging the gap between computational models on different scales. He or she is further expected to play an active role in the newly founded *'Center for Multiscale Modeling and Simulation'* at the FAU.

Qualifications include university undergraduate and doctoral degrees, excellent teaching skills, and a habilitation or equivalent other qualification, which may have been gained outside the University or within a "Junior Professorship".

At the time of appointment the candidate must not be older than 52 years of age. The Ministry for Science, Research and Art may allow an exception in special cases, which has to be approved by the Ministry of Finance (cf. art. 10 parag., 3, s.2 of the Bavarian Law on Personnel at Institutions of Higher Education).

The University of Erlangen-Nuremberg actively encourages applications from female candidates in an effort to increase female representation in research and teaching.

Applications from the severely disabled having the same suitability for appointment as other candidates will be given priority.

The position is to be filled by November 1, 2008.

Application documents (curriculum vitae, photograph, list of publications and teaching activities, certified copies of degree certificates and copies of the five (5) most important publications) and a brief statement of research interests must be sent four weeks after publication to: Prof. Dr. W. Peukert, Institute of Particle Technology, Cauerstraße 4, D-91058 Erlangen, Germany.

Friedrich-Alexander-University Erlangen-Nuremberg

www.uni-erlangen.de

NORTHWESTERN
UNIVERSITY

Investigator
Cardiovascular Research
and Regenerative Medicine

The Feinberg Cardiovascular Research Institute (FCVRI) at Northwestern University's Feinberg School of Medicine is recruiting for a full-time tenure-track position at the Assistant, Associate, or Professor level. Applicants should have a MD (BC/BE in Cardiology) and/or Ph.D. Candidates with research interests in regenerative medicine, gene therapy, stem cell biology, proteomics, and translational research are particularly encouraged to apply. Candidates at the Associate and Professor levels are expected to maintain a robust NIH-funded laboratory and contribute to the visibility of FCVRI through publications in high-impact life sciences journals.

Successful applicants will receive a competitive starting salary and generous start-up package. The start date is negotiable. Applications must be received by **April 15, 2008** for full consideration. Please send CV, description of research interests, and names of at least three references to:

Douglas W. Losordo, MD
Director, Feinberg Cardiovascular Research Institute
Northwestern University
303 E. Chicago Avenue
Tarry 12-703
Chicago, IL 60611-3308

Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

FACULTY POSITION IN CANCER PREVENTION

The University of Texas M. D. Anderson Cancer Center, Science Park- Research Division, seeks outstanding basic and/or translational scientists with research interests in cancer prevention for a tenure-track Assistant Professor position. Applications are welcomed from individuals utilizing novel molecular, cellular and/or animal model systems focused on organ-specific or pathway-specific approaches to mechanism-based cancer prevention. Areas of interest include, but are not limited to, target identification, carcinogenesis intervention, nutrition/gene interactions, metabolism/energy balance and inflammation/immune responses. Preference will be given to candidates interested in working in a highly collaborative, interdisciplinary environment with interests complementing those of departmental faculty. M. D. Anderson offers an outstanding research environment and a highly competitive recruitment package is available. The successful candidate will be expected to develop and maintain a world-class externally funded research program and to participate in graduate student training. Required qualifications include Ph.D. and/or M.D. and demonstrated scholarly research experience.

Information about Science Park can be found at: **http://sciencepark.mdanderson.org/**

Interested candidates should submit a statement of research interests, CV and contact information for 3 references to:

Susan M. Fischer, Ph.D.
Department of Carcinogenesis
Chair, Search Committee, at:
mfendley@mdanderson.org

Application deadline: March 21, 2008

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History®

M. D. Anderson Cancer Center is an equal opportunity employer and does not discriminate on the basis of race, color, national origin, gender, sexual orientation, age, religion, disability or veteran status except where such distinction is required by law. All positions at The University of Texas M. D. Anderson Cancer Center are security sensitive and subject to examination of criminal history record information. Smoke-free and drug-free environment.

Department of Microbiology and Molecular Genetics
Faculty Position in Cancer Research

MEDICAL COLLEGE OF WISCONSIN

Candidates are invited to apply for a tenure-track Assistant Professorship; outstanding candidates of higher rank will also be considered. Scientists interested in the molecular genetic mechanisms that lead to cancer are encouraged to respond; those investigators studying cell cycle control or genomic instability are of particular interest. This is a joint recruitment with the Cancer Center.

The Department is in a phase of growth and expansion with strong research programs in molecular genetics, host/pathogen interactions, and inflammation. These initiatives are complemented by college-wide investment in multiple research areas including cancer research and human and molecular genetics. The successful applicant will join a collegial group of interactive, well-funded and productive investigators and will be expected to establish a strong, independent research program and participate in graduate and medical student teaching. Competitive salary support, start-up funds and renovated laboratory space will be provided; many state-of-the-art core facilities are also available. A PhD and/or MD degree and post-doctoral experience are essential.

Applications will be considered as they arrive but should be received by **March 14, 2008**. Applicants should submit a *curriculum vitae*, statement of research interests, and the names of three references to: **Dr. Paula Traktman, Chairman, Dept. of Microbiology and Molecular Genetics, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226**. E-mail: **kthompso@mcw.edu**.

http://www.mcw.edu/microbiology

EEO/AA/M/F/D/V

MICHIGAN STATE
UNIVERSITY

Director of the Division of Reproductive Biology
Department of Obstetrics, Gynecology and Reproductive Biology

The Department of Obstetrics, Gynecology and Reproductive Biology in the College of Human Medicine at Michigan State University seeks outstanding candidates for the Directorship of the Division of Reproductive Biology. Qualifications include an earned M.D. or PhD in a relevant specialty.

Applicants are expected to have a successful track record of sustained, collaborative, peer-reviewed funding and publications in topics related to women's health, and to maintain an active research program, with preference given to NIH funding. The successful candidate will have the opportunity, authority and resources to develop and oversee basic and translational research within the department and to develop research programs with the Van Andel Institute and Spectrum Health Research Institute.

The mission of the Division of Reproductive Biology is to understand the mechanisms of diseases relevant to women's health and translate that understanding into novel therapies.

Applicants who are not U.S. citizens or permanent residents must provide documentation evidencing employment authorization in the United States. Applications/nominations should include a current curriculum vitae and personal statement. Electronic submission of applications is preferred. The review of applications will begin on January 2, 2008, and will continue until the position is filled. Salary and rank will be commensurate with experience.

All applications and inquiries will be confidential. Direct correspondence and inquiries to: **Richard E. Leach, MD. FACOG, FACS, Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Biology, College of Human Medicine, Michigan State University, Richard.Leach@hc.msu.edu.**

Michigan State University is committed to achieving excellence through cultural diversity. The university actively encourages applications and/or nominations from women, persons of color, veterans and persons with disabilities.

MSU IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY EMPLOYER.

UNIVERSITY OF MINNESOTA
INSTITUTE FOR TRANSLATIONAL NEUROSCIENCE
Translational Neuroscience Scholars Program
Multiple Faculty Positions

The Institute for Translational Neuroscience (ITN) at the University of Minnesota is seeking to hire up to eight tenure or tenure-track faculty members to enhance research strengths in the neurodegenerative and neuromuscular diseases. The vision for these positions is to provide significant endowment-like recurring salary support so the most accomplished scientists will be able to focus on their research. The newly established ITN will recruit neuroscientists and physicians with Ph.D. and/or M.D. degrees at the Assistant, Associate or Full Professor level. Areas of interest include, but are not limited to, Alzheimer's disease, ataxia, Parkinson's disease, ALS and muscular dystrophy. Translational Neuroscience Scholars will be affiliated with the Grossman Center for Memory Research and Care, the Wellstone Muscular Dystrophy Center, or the Center for Neurological Research. We are particularly interested in candidates using animal models of dementia, movement disorders, and neuromuscular disease, as well as candidates who directly study human degenerative neurological diseases. The key criteria are superlative scientific accomplishment and the promise of future research impact. Successful candidates must demonstrate the capability to establish a vigorous, externally funded research program, a commitment to medical, graduate or undergraduate education, and leadership through vision and collaborative program development.

Successful new recruits will receive substantial recurring salary support, an excellent startup package, and laboratory space in a newly built, integrated neuroscience research complex housing the Grossman Center for Memory Research and Care, the Wellstone Muscular Dystrophy Center, the Center for Neurological Research, the Center for Magnetic Resonance Research, the Center for Orphan Drug Research, and the Stem Cell Institute. Departmental affiliation will be determined by the applicant's interest and the relevance of the applicant's research program to departmental goals. For Assistant level appointments, candidates are expected to have doctoral and postdoctoral training in the neurosciences and research accomplishments consistent with developing a nationally recognized and independent research program. Associate or Full Professor appointments will require demonstrated independence and research productivity, including a strong track record of major external funding and peer-reviewed publications. Candidates must be U.S. citizens or be able to secure permanent residence status. The starting date is negotiable, with appointments available as soon as June 1, 2008. The University of Minnesota is committed to diversifying its faculty and encourages applications from women and minorities.

Review of applications will commence **January 31, 2008**, and continue until the positions are filled. Applicants should send curriculum vitae, statement of research interests and intentions, and three letters of reference to: **ITN Faculty Search Committee, Attention: Rosalyn Segal, Medical School Dean's Office, MMC 293, 420 Delaware Street S.E., Minneapolis, MN 55455. Email: rsegal@umn.edu**. Electronic versions of the required information may be e-mailed but must be followed with a hard-copy for the official search files.

The University of Minnesota is an Equal Opportunity Educator and Employer.

UNIVERSITY *of* NEW HAMPSHIRE

Associate Dean of Research

The **University of New Hampshire**, College of Life Sciences and Agriculture, seeks an **Associate Dean of Research**. Reporting to the Dean, the ideal candidate will have a record of distinguished research and education achievement that warrants appointment as a tenured faculty member; a demonstrated ability in management of large research programs and development of interdisciplinary research projects; a commitment to undergraduate and graduate education; excellent communication and interpersonal skills; and a commitment to the principles of diversity.

Applicants should submit Curriculum Vitae; 1-2 page vision statement on research, education, and outreach; names and contact information of four references to: **Kimberly J. Babbitt, Search Committee Chair, 215 James Hall, 56 College Road, University of New Hampshire, Durham, NH 03824.** Review of applications will begin 2/15/08 and continue until the position is filled.

For more information go to:
http://www.colsa.unh.edu/employment/index.html.

The University actively seeks excellence through diversity and application by members of all underrepresented groups is encouraged.

Endowed Chair and Department Head
Department of Physiology
Louisiana State University Health Sciences Center
School of Medicine
New Orleans

LSU Health Sciences Center

The Louisiana State University Health Sciences Center School of Medicine in New Orleans invites applications and nominations for Head of the Department of Physiology and the Kenneth A. Ardoin/Pfizer Super-chair of Basic Cardiovascular Research. The successful candidate will be responsible for all facets of activity in the department, including both graduate and undergraduate medical education, faculty recruitment and retention, and development of research programs. The successful candidate will have a PhD, MD or MD/PhD, will be internationally recognized for research in Physiology, Systems Biology or Cell/Molecular Physiology and will have an exceptional record of extramural research funding.

The applicant will be expected to coordinate the development of program project grants and training programs within the department and also to foster translational research. He/she must demonstrate leadership ability, a commitment to biomedical research and education and have the ability to provide a vision of excellence for the Department. Achievements in multi-disciplinary collaborative research, mentorship, teaching, and administration that promote an inclusive environment are essential.

Candidates will have opportunities to interact with Centers of Excellence, including the Cardiovascular Center, the Alcohol Research Center, the Neuroscience Center, the Stanley S. Scott Cancer Center, and the Gene Therapy Program. Excellent core facilities are also available.

Significant resources will be available for departmental development, and faculty recruitment and start-up. Candidates must qualify for the rank of tenured Professor in accordance with School of Medicine and LSU System criteria; the compensation package will be competitive.

Candidates should provide their Curriculum Vitae, including a full list of publications, a brief statement of educational, research, service, and administrative interests, and a vision statement describing goals for departmental development. These materials should be forwarded electronically to: **Dr. Wayne L. Backes, Associate Dean for Research, LSUHSC School of Medicine, 533 Bolivar St., New Orleans, LA 70112; MSfacultyrecruit@lsuhsc.edu.** Review of applications will commence immediately and will continue until the position is filled.

LSUHSC is an Equal Opportunity/Affirmative Action Employer.

FACULTY POSITIONS

RUPRECHT-KARLS-
UNIVERSITÄT
HEIDELBERG

The Medical Faculty Mannheim of the University of Heidelberg is seeking qualified applicants for the position of

Professor of Child and Adolescent Clinical Psychopharmacology Eli Lilly - Endowed Professorship (W3)

The incumbent will represent the field as a whole in terms of research and teaching. Since this is an endowed professorship limited to five years of funding the position is non-tenure track.

Research facilities are provided at the Central Institute of Mental Health in Mannheim (Foundation under Public Law, Director: Andreas Meyer-Lindenberg, MD, PhD, MSc) within the Department of Child- and Adolescent Psychiatry and Psychotherapy (Medical Director: Tobias Banaschewski, MD, PhD).

Applicants should show a high quality research profile with extensive clinical research experience on an international level. A postdoctoral thesis (habilitation) or its equivalent is expected. Candidates should be board-certified in Child- and Adolescent Psychiatry and Psychotherapy and possibly also have acquired additional qualifications in related areas such as Psychosomatic Medicine, Psychotherapy or Psychology. Applicants should ideally also have outstanding experience in planning, conducting and publishing clinical research in the area of childhood, adolescent and adult psychopharmacology as well as in soliciting government or industry sponsored third party funding. Within the context of his/her clinical research activities the incumbent will also be involved in inpatient and outpatient medical care.

By establishing this chair and through the appointment of its incumbent the university aims to strengthen research activities in the area of clinical psychopharmacology within the field of child- and adolescent psychiatry. A major focus of the professorship will be on translational research and the transfer of knowledge between academic institutions and the industry.

In addition to fulfilling its university and clinical functions (Dept. of Psychiatry and Psychotherapy, Dept. of Child and Adolescent Psychiatry and Psychotherapy, Dept. of Psychosomatic and Psychotherapeutic Medicine, Dept. of Addictive Behavior and Addiction Medicine as well as the Chair for Neuropsychology and Clinical Psychology) the Central Institute of Mental Health is known as a research institute of international ranking (WHO Collaborating Center, Member of the Association for Clinical and Biomedical Research, as well as recipient of special research funding – presently SFB 636 on neuronal plasticity). The institute is home to a wide range of research areas such as the departments/working groups on Biostatistics, Community Psychiatry, Genetic Epidemiology, Geriatric Psychiatry, Clinical Psychology, Molecular Biology, Neuroimaging, NMR research and Psychopharmacology, thus offering ample opportunity for the integration of the applicant's own research activities.

By law the appointment is limited to five years.

The University of Heidelberg is seeking to increase the percentage of female scientists and is explicitly encouraging qualified female scientists to apply. The University is an equal opportunity employer. Applications from qualified disabled persons will be given priority.

Applications containing all pertinent information should be sent within two weeks to: **Medical Faculty Mannheim, University of Heidelberg, Dean's Office, Klaus van Ackern, MD, PhD hon., University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany**

FACULTY POSITIONS IN CELL SIGNALING
University of Texas Medical School – Houston

The Department of Integrative Biology and Pharmacology in the University of Texas Medical School at Houston has tenure track faculty openings for researchers with a focus on the cell biology, physiology and pharmacology of cell signaling. Appointments will be at the Assistant Professor level for candidates completing their postdoctoral training, or at the Associate Professor level for candidates with funded, independent research programs. Applicants using innovative *in vitro* or animal model systems, or computational and systems approaches to study cell signaling and/or physiological regulatory mechanisms will be given preference. Responsibilities include the development of a funded, internationally recognized research program that complements existing research activities in the department (**http://ibp.med.uth.tmc.edu**) and participation in medical and graduate education. The Medical School is located within the Texas Medical Center, which includes UT- Houston Health Sciences Center, Baylor College of Medicine and M.D. Anderson Cancer Center. Attractive start-up packages and competitive salaries and benefits will be provided.

Send a *curriculum vitae*, a description of future research plans and at least three letters of reference to **Dr. John F. Hancock, Department of Integrative Biology and Pharmacology, University of Texas Medical School at Houston**, by email at **ms.ibp.applicants@uth.tmc.edu** or by mail to **P.O. Box 20708, Houston, TX 77225**. Review of applications will begin immediately and will continue until the positions are filled.

The University of Texas is an Equal Opportunity/ Affirmative Action Employer. M/F/D/V. This is a security sensitive position and thereby subject to Texas Education Code § 51.215. A background check will be required for the final candidate.

POSITIONS OPEN

John Innes Centre

Independent Research Fellowships

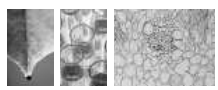
The John Innes Centre (JIC), Norwich, UK is a world leading centre of excellence in plant and microbial sciences based on the Norwich Research Park. We are inviting applications from outstanding researchers who either hold, or wish to apply for Independent Research Fellowships, to attend a Conference at the JIC on 2/3 June 2008. At the meeting you will be able to present a talk about your proposed area of research and to discuss your proposals, the development of your group and your future career plans in depth with senior JIC Scientists.

After the Conference we will select and mentor outstanding candidates in writing. Fellowship applications and/or offer the opportunity to move existing Fellowships to the JIC.

Further details and particulars can be found at http://www.jic.ac.uk/corporate/opportunities/vacancies/fellows.htm

Please e-mail a 2-page summary of your research plan, a copy of your CV and arrange for these letters of recommendation to be emailed to dawn.barrett@bbsrc.ac.uk by Friday 18th April 2008.

The John Innes Centre is a registered charity (No223852) grant-aidedby the Biotechnology and Biological Sciences Research Council and is an Equal Opportunities Employer.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
OFFICE OF THE DIRECTOR
OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES
DIVISION OF RESOURCE DEVELOPMENT AND ANALYSIS

The Office of the Director, National Institutes of Health (NIH) in Bethesda, Maryland, is seeking a Director of the Division of Resource Development and Analysis (DRDA) within the Office of Portfolio Analysis and Strategic Initiatives (OPASI). If you are an exceptional candidate with an M.D. and/or Ph.D., we encourage your application.

The OPASI's primary objective is to develop: a transparent process of planning and priority-setting characterized by a defined scope of review with broad input from the scientific community and the public; valid and reliable information resources and tools, including uniform disease coding and accurate, current and comprehensive information on burden of disease; an institutionalized process of regularly scheduled evaluations based on current best practices; the ability to weigh scientific opportunity against public health urgency; a method of assessing outcomes to enhance accountability; and a system for identifying areas of scientific and health improvement opportunities and supporting regular trans-NIH scientific planning and initiatives.

As the DRDA Director, you will be responsible for employing resources (databases, analytic tools, and methodologies) and developing specifications for new resources, when needed, in order to conduct assessments based on NIH-owned and other databases in support of portfolio analyses and priority setting in scientific areas of interest across NIH.

Salary is commensurate with experience and includes a full benefits package. A detailed vacancy announcement with the mandatory qualifications and application procedures can be obtained on **USAJOBS at www.usajobs.gov** (announcement number **OD-08-236976-T42**) and the NIH Web Site at **http://www.jobs.nih.gov**. Questions on the application procedures may be addressed to Brian Harper on 301-594-5332. Applications must be received by midnight eastern standard time on **February 14, 2008**.

This position is subject to a background investigation.

DHHS and NIH are Equal Opportunity Employers

FACULTY POSITIONS

Chair and Professor
Washington State University
Department of Horticulture and Landscape Architecture

Washington State University - Department of Horticulture and Landscape Architecture, Chair and Professor. 12-month tenured position (Professor). **Required:** Doctorate in horticultural science, landscape architecture, plant sciences, or a related discipline; an overall record tenurable at full professor rank; a record of excellence in leadership in at least two of the following four areas: (1) research, scholarly, or creative practice, (2) teaching, learning, or interactive communication, (3) outreach, extension, or service activities, (4) academic administration; proof of excellence in leadership, attracting competitive funding, promoting productive teamwork, and facilitating and developing the full potential of diverse individuals and disciplines; evidence of successful financial management, including the generation and allocation of resources; demonstrated abilities in consensus building, strategic planning and implementation, development activities, and communication with and among diverse stakeholder and constituency groups.

For full position description listing all qualifications and application process, visit: **http://www.hrs.wsu.edu/employment/fapvacancies.aspx** (Search #**4946**). Contact: **Dr. Pete W. Jacoby, c/o Beverly Brantner, Dept. of Horticulture and Landscape Architecture, WSU, P.O. Box 646414, Pullman, WA 99164-6414. brantner@wsu.edu, 509-335-3943, Fax 509-335-8690**. Screening: **March 15, 2008**.

EEO/AA/ADA

Senior Cancer Researcher

The Jackson Laboratory

Leading the search for tomorrow's cures

The Jackson Laboratory, a world-renowned mammalian genetics research institution and NCI-designated Cancer Center, is seeking an experienced **Senior Cancer Researcher** to assist in the expansion of the laboratory's Cancer Center Program. We are looking for a leader with a global view of cancer research, who can facilitate interdisciplinary and translational approaches while conducting a competitive, independently funded research program.

Candidates should have the following minimum qualifications:

- Extensive knowledge of cancer biology, a Ph.D. or M.D., and at least 10 years of independent research experience
- Strong scientific, organizational, management, and interpersonal communication skills
- The ability to interact effectively with internal scientists, external collaborators, as well as granting agencies
- Willingness and ability to recruit and mentor several new faculty members

We offer a unique scientific research environment, including excellent collaborative opportunities within our faculty, unparalleled mouse genomic resources, outstanding core scientific support services, highly successful pre- and postdoctoral training programs, a major scientific meeting center featuring courses and conferences centered on mouse models, and an idyllic research environment surrounded by Acadia National Park.

For information, go to: www.jax.org and www.jax.org/research/cancer_center.html

Applicants should send a curriculum vitae and a brief summary of their research to:

Robert Braun, Associate Director and Chair of Research
The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609

Interested individuals can also send an email to: **bob.braun@jax.org**

Applications should be received no later than **March 1, 2008.**

The Jackson Laboratory is an EOE/AA employer.

www.jax.org

ASSISTANT to FULL PROFESSOR
Program in Genetics and Genomic Medicine
University of Maryland School of Medicine

The interdepartmental Program in Genetics and Genomic Medicine (PGGM) at the University of Maryland School of Medicine is seeking faculty candidates whose backgrounds and experience will support appointments on the tenure track or with tenure. Qualified candidates can be from any field of biomedical science (including neuroscience, molecular pathology, medicine, pediatrics, and cancer) and should have expertise in human genetics, genetic epidemiology, molecular genetics (including model systems), statistical genetics, bioinformatics, pharmacogenomics, functional genomics, or related fields. Appointments of successful candidates will be in the appropriate basic and/or clinical departments, and offer outstanding opportunities for independent and collaborative research in a highly interactive, multidisciplinary environment at the University of Maryland, Baltimore. Funded candidates preferred. Please send curriculum vitae and names of four references to: **Alan R. Shuldiner, M.D., Director, Program in Genetics and Genomic Medicine, University of Maryland School of Medicine, c/o JoAnn Gibbs, Room N3E10, University of Maryland Medical Center, 22 S. Greene Street, Baltimore, MD 21201.** Please cite positions 03-309-462/485. *The UM,B is an Affirmative Action/Equal Employment Opportunity/ADA Employer and encourages applicants from diverse racial, ethnic, and cultural backgrounds to apply.*

The Department of Chemistry at Wellesley College invites applications for a tenure-track faculty position in physical chemistry at the rank of first-level **ASSISTANT PROFESSOR.** The position will begin in September 2008. We are seeking candidates who are strongly committed to excellence in both teaching and research in a liberal arts environment. Candidates will be expected to teach courses at all levels of the chemistry curriculum as well as the Environmental Studies Program. Candidates who have plans for an active research program involving undergraduate students in laser spectroscopy are strongly encouraged to apply. A Ph.D. is required and postdoctoral experience is desirable.

Applications, including a cover letter; a statement of teaching experience, interests, and philosophy; a statement of research interests; curriculum vitae; and three letters of recommendation from individuals familiar with your academic and professional background, should be sent, in Word or, preferably, PDF format, to **e-mail: chem08search@wellesley.edu.** All materials must be submitted electronically. The deadline for receipt of all application materials is February 1, 2008.

Wellesley College is an Equal Opportunity/Affirmative Action Educational Institution and Employer. The College is committed to increasing the diversity of the faculty and the curriculum. Candidates who believe they will contribute to that goal are strongly encouraged to apply.

ECOHYDROLOGY

The University of Vermont seeks to hire an outstanding **ASSISTANT or ASSOCIATE PROFESSOR of ENGINEERING, MATHEMATICS, or COMPUTER SCIENCE** with emphasis on complex systems analysis in the context of ecohydrology, the linkage between hydrological and ecological systems. The hire is part of a University focus on the environment and a College initiative in complex systems.

Qualifications for the position include an earned Doctorate, a proven record of scholarly activities, and the ability to teach relevant graduate and undergraduate courses. Successful candidates will be expected to make significant and balanced contributions to research, teaching, and service, including the development of a nationally respected, externally funded research program.

Preference given to complete applications received before February 20, 2008. Submit curriculum vitae, statement of research and teaching interests, and contact information for three references to **website: http://www.uvmjobs.com** (requisition #032225). *Affirmative Action/Equal Opportunity Employer.*

CANCER RESEARCH

The University of South Carolina (USC) in Columbia, South Carolina, and the Medical University of South Carolina (MUSC) in Charleston, South Carolina, are jointly seeking applications for a tenure-track position at the rank of **ASSISTANT/ASSOCIATE PROFESSOR** on the Columbia campus **(website: http://www.sccp.sc.edu).** The candidate will have a Ph.D. degree, postdoctoral experience, and research interests in cancer pharmacology or cell biology, cancer drug discovery, or colorectal cancer. The applicant will be expected to develop a strong, NIH-funded research program and participate in professional and graduate education. Candidates hired at the rank of Associate Professor will have a funded research program. Pharmacy faculty are members of the NIH-funded Center for Colon Cancer Research **(website: http://www.cccr.sc.edu),** South Carolina Cancer Center, Hollings Cancer Center in Charleston, and Centers for Drug Discovery and Cancer Therapeutics.

Interested candidates should submit curriculum vitae, statement of research interests, and the names of three references to: **Dr. Michael Wyatt, Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC 29208 (e-mail: wyatt@sccp.sc.edu).** Electronic submission is encouraged. Review of applications will begin on February 22, 2008, and will continue until the position is filled.

The University of South Carolina and the Medical University of South Carolina are Affirmative Action/Equal Opportunity Employers.

FACULTY POSITION in IMMUNOLOGY

The University of Minnesota (UM) Medical School, Duluth invites applications for a faculty position with a research focus in the area of immunology. Candidates must have a Ph.D., M.D., D.V.M., or equivalent degree, postdoctoral experience (including peer-reviewed publications), and teaching experience, preferably in the area of immunology. Preference will be given to individuals conducting research in the areas of neuroimmunology or inflammation. Faculty rank is open, including **ASSISTANT, ASSOCIATE, or FULL PROFESSOR;** the appropriate rank will be based on applicant qualifications and determined at the time of hire. Candidates will be expected to lead an innovative, extramurally funded research program in immunology.

The mission of the Medical School, Duluth is to be a leader in educating physicians dedicated to family medicine, to serve the health care needs of rural Minnesota and American Indian communities, and to discover and disseminate knowledge through research. Opportunities exist to participate in undergraduate, graduate (M.S. and Ph.D.), and allied health student education. Close relationships with faculty in the University of Minnesota Academic Health Center and the UM College of Pharmacy, Duluth also provide excellent opportunities for research collaborations. Duluth is located on the scenic north shore of Lake Superior just south of the Boundary Waters wilderness area, and offers an outstanding quality of living and numerous recreational opportunities.

Applications are made online at **website: http://employment.umn.edu** (requisition #153226). To ensure consideration, a cover letter, a statement of teaching philosophy and a research plan (one page maximum each), curriculum vitae, and the names and contact information of three references should be directed to: **Jon Holy, Ph.D., Chair of the Search Committee,** via the online process. Three letters of recommendation should be sent under separate cover to: **Lurinda Isaacson, 1035 University Drive, 113 SMed, Duluth, MN 55812-3031,** or **e-mail: lisaacso@d.umn.edu.** *The University of Minnesota is an Equal Opportunity Educator and Employer.*

FACULTY POSITIONS in ENTOMOLOGY
The University of Georgia

The Department of Entomology at the University of Georgia seeks to fill two positions at the level of **ASSISTANT or ASSOCIATE PROFESSOR** in the study of parasite or microbial-insect interactions. Areas of interest include pathogenic or symbiotic associations as well as studies on vector species in animal or plant systems. Candidates using innovative approaches in either the molecular sciences or ecology will be carefully considered. Microbiology, Parasitology, and Infectious Diseases are growing Programs at the University of Georgia; expertise in entomology and elsewhere on campus offers unique collaborative potential in genetics, genomics, parasitology, ecology, and evolution. Applicants must have a Ph.D. degree (or equivalent) and suitable experience. Successful candidates will be expected to establish a strong extramurally funded research program and contribute to instruction in the Department. To apply, submit a cover letter, curriculum vitae, and a description of research and teaching interests to **e-mail: entomolo@uga.edu** (open search in the subject line). Applicants should arrange to have three letters of reference sent to: **Open Search Committee, c/o Dr. M.R. Strand (Chair), Department of Entomology, University of Georgia, 413 Biological Sciences, Athens, GA 30602-2603.** Complete applications received by March 31, 2008, are assured of full consideration. *The University of Georgia is an Affirmative Action/Equal Opportunity Employer committed to increasing diversity of its faculty and students.*

SINGLE MOLECULE BIOLOGIST
Norris Comprehensive Cancer Center
Keck School of Medicine
University of Southern California

The Norris Comprehensive Cancer Center, the Department of Biochemistry and Molecular Biology, and the Department of Biological Sciences are recruiting for a tenure-track position at the **ASSISTANT, ASSOCIATE, or FULL PROFESSOR** level. We seek scientists with an innovative research program in the analysis of single molecules of biological interest. The successful candidate will receive a generous startup package, will be housed either in the newly constructed Harlyne Norris Tower of the Norris Comprehensive Cancer Center, and will be a member of the Cancer Center.

In addition, as a member of the structural biology group of University of Southern California, the candidate will have available a 700 megahertz Bruker nuclear magnetic resonance machine, an X-ray crystallography facility, a biophysics core, and other state-of-the-art equipment. The successful candidate will have an academic appointment in the Department of Biochemistry and Molecular Biology, and a joint appointment in the Department of Biological Sciences.

Applicants should submit curriculum vitae, a research plan, and three letters of reference to **Ms. Isabel Lora** at **e-mail: lora_m@ccnt.usc.edu.** *Women and minority candidates are encouraged to apply. USC is an Equal Opportunity/Affirmative Action Employer.*

PROFESSORSHIP in ECOLOGY, EVOLUTION, and/or BEHAVIOR. Princeton University's Department of Ecology and Evolutionary Biology seeks a visionary senior scientist who will prosper in an interdisciplinary environment spanning ecology, evolution, and behavior. Area of expertise is open, but a demonstrated record of excellence in research, teaching, and mentoring (at undergraduate and graduate levels) is essential. Applications, curriculum vitae, and names of three referees, should be sent to: **Prof. Dan Rubenstein, Chair, Department of Ecology and Evolutionary Biology, Guyot Hall, Princeton University, Princeton, NJ 08544-1003.** Screening of applications will begin 15 February 2008, and continue until the position is filled. For general application information and how to self-identify, see **website: http://www.princeton.edu/dof/ApplicantsInfo.htm.**

Princeton University is an Equal Opportunity Employer and complies with applicable Equal Employment Opportunity and Affirmative Action regulations.

Pfizer

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Discoveries

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We are Pfizer Global Research & Development, Pfizer's visionary discovery and development division and the largest pharmaceutical research & development organization in the world. Our mission is to discover and deliver a growing variety of medicines and improve the health and quality of life for people around the world.

To date, PGRD has brought to market a wide range of ground-breaking medicines, such as Lipitor® (atorvastatin calcium), Zithromax® (azithromycin), Viracept® (nelfinavir mesylate), Zoloft® (sertraline hydrochloride), Viagra® (sildenafil citrate), and our newest smoking cessation medicine, Chantix® (varenicline). And, today, with a broad research pipeline that spans many therapeutic areas, we are determined to bring even more cures to the marketplace.

> *"We have all the right tools, all different levels of scientists, and a good balance of opportunities throughout the world to allow us the benefit of researching and experimenting to potentially discover drugs. And discovering drugs is our ultimate purpose," states Elva P.*

With 99 total programs, our pipeline includes 20 potential treatments for cancer; 16 for cardiovascular, metabolic and endocrine diseases; 17 for pain and inflammation; 17 for neurological disorders, 10 for infectious diseases, and 19 in other areas including genitourinary, ophthalmology, dermatology and allergy/respiratory. Included in this portfolio is a total of 14 biologic compounds, including vaccines and antibodies designed to treat cancer, rheumatoid arthritis, influenza and other serious medical conditions.

> *"From HIV aids drug support to CNS system drugs, we really have major drugs that have significantly improved the livelihood of individuals across the world regardless of economic status," explains Tiffini B.*

But there is much more work to be done, and we at Pfizer will take the challenges facing global healthcare head-on.

Your talent can change the world. Join us and help turn discoveries into miracles.

To apply or to learn more about our people, our products, and our plans for the future visit **www.pfizer.com/careers**

We're proud to be an equal opportunity employer and welcome applications from people with different experiences, backgrounds and ethnic origins.

National Heart Lung and Blood Institute

Tenure-Track/Tenured Position
Clinical Translational Research

The Division of Intramural Research of the National Heart, Lung and Blood Institute seeks an individual to direct an independent clinical or translational research program in the heart, lung or blood diseases. The successful candidate would develop a program to complement and integrate with existing research in Bethesda. An M.D. or M.D./ Ph.D. degree and record of research accomplishments as evidenced by publications in major peer-reviewed journals are required. This position comes with generous start up funding, as well as stable intramural personnel and budget support. There is access to advanced core facilities, including large research hospital at the NIH Clinical Research Center; a pharmacy development service; a transgenic and knockout mouse facility; confocal and electron microscopy cores; a multi-modality non-invasive mouse imaging facility; siRNA resources; an advanced fluorescent activated cell sorting facility; and state of the art genomics, microarray and proteomics.

A competitive salary commensurate with experience and qualifications is offered. **Appointees may be US citizens, resident aliens or non-resident aliens with or eligible for a valid employment visa**. Applications must be received by **February 15, 2008**. Please submit a curriculum vitae and brief statement of research interests along with three letters of reference to:

Neal S. Young, MD, Chief, Hematology Branch, NHLBI, NIH, c/o Ms. Sheree Hawkins, Building 10, Room 7N220, 10 Center Drive, Bethesda, MD 20892.

You may apply using one of the following methods:

1. Mail application package to address listed above
2. Email your application to **hawkinss@mail.nih.gov**
3. Apply on-line at **http://www.training.nih.gov**
    a. click on NIH Science Jobs
    b. click on Current NIH Tenure-Track and Tenured Openings
    c. click on Tenure Track-Tenured Position Clinical Translational Research
    d. click on Apply

National Heart Lung and Blood Institute

Staff Scientist

The National Heart, Lung and Blood Institute, a major component of the NIH and the DHHS, is recruiting for a Staff Scientist within the Molecular Biology Section of the Translational Medicine Branch. The successful candidate would join a group of investigators examining the molecular and cellular biology of mitochondrial regulation in the development of cardiovascular diseases and diabetes. Applicants should have a Ph.D. and/or a M.D. with experience in advanced molecular and cellular biology. Prior studies involving proteomics, expertise in viral vector work and experience with transgenic mice would be advantageous.

The focus of the research is to augment our understanding how the mitochondrion is regulated at the molecular level to modulate cardiac and skeletal muscle function in diabetes. Retrograde signaling from the mitochondria to nucleus as a component in this regulation is also being explored. The research work will integrate genetic, proteomic and biochemical approaches in animal disease models and/or in cell culture.

Salary is commensurate with research experience and accomplishments. Applicants should send a CV, a brief statement of research interests, and the names and contact information of three references, by **February 25, 2008** to:

Michael N. Sack, M.D., Ph.D., Investigator – Translational Medicine Branch, Bldg. 10, CRC, Room 5-3150, 10 Center Drive, Bethesda, MD 20892-1454, USA, Fax: 301-480-4599, Email: sackm@nhlbi.nih.gov.

National Heart Lung and Blood Institute

Staff Scientist

The National Heart, Lung and Blood Institute, a major component of the NIH and the DHHS, is recruiting for a Staff Scientist within the Molecular Biology Section of the Translational Medicine Branch. The successful candidate would join a group of investigators examining the molecular and cellular biology of vascular regeneration and vascular wound repair in vascular diseases. Applicants should have a Ph.D. and/or a M.D. with experience in advanced molecular and cellular biology. Prior studies in vascular biology, immunology and conditional knock out mice models would be advantageous.

The focus of the research is to augment our understanding of the complex interaction of local vascular cells, vascular progenitor cells and infiltrating inflammatory cells during vascular remodeling. The research work will integrate advanced tissue imaging, array approaches and conditional lineage/pathway tracing and knock out animal models.

Salary is commensurate with research experience and accomplishments. Applicants should send a CV, a brief statement of research interests, and the names and contact information of three references, by **February 20, 2008** to:

Manfred Boehm, M.D., Investigator –Translational Medicine Branch, Bldg. 10, CRC, Room 5-3132, 10 Center Drive, Bethesda, MD 20892-1454, USA, Fax: 301-451-7090, Email: boehmm2@mail.nih.gov.

WWW.NIH.GOV

Clinical Director
National Institute of Neurological Disorders and Stroke
National Institutes of Health

The Division of Intramural Research of the National Institute of Neurological Disorders and Stroke (NINDS) announces a search for a Director of Clinical Research. The Clinical Director will be responsible for the leadership of all aspects of the intramural NINDS clinical program and direct an active and independent research program. The Clinical Director will play a key role in the significant expansion of clinical research which is planned over the next five years. This expansion is aimed at strengthening the existing programs, making broader connections to other clinical programs at NIH, as well as increasing integration with the excellent basic neuroscience research programs in NINDS. The Institute has a strong interest in increasing therapeutics research aimed at relieving the burden of neurological disease. NINDS presently has clinical programs in neurogenetics, neuroimmunology, movement disorders/cortical physiology and stroke, as well as an active surgical neurology program and an active neuroimaging program. The extraordinary resources available at the NIH Clinical Research Center, the world's largest research hospital, and the unfettered focus on research at the NIH makes this a unique opportunity. The successful candidate for this tenured position will have already established an international reputation for clinical neuroscience research as well as have demonstrated skills in building clinical programs. Application for this position should be sent to: **Dr. Story Landis, Director, NINDS, c/o Peggy Rollins, Building 35, Room GA908, NINDS, NIH, Bethesda, MD 20892-3716**. Evaluation of applications will begin **March 25, 2008**. The NINDS is one of the Institutes of the National Institutes of Health, a component of the Department of Health and Human Services.

OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES
DIRECTOR, DIVISION OF EVALUATION AND SYSTEMIC ASSESSMENTS

The Office of the Director, National Institutes of Health (NIH) in Bethesda, Maryland, is seeking a Director of the Division of Evaluation and Systemic Assessments (DESA) within the Office of Portfolio Analysis and Strategic Initiatives (OPASI). If you are an exceptional candidate with an M.D. and/or Ph.D. and the vision and ability to integrate evaluation systems and programs across multiple disciplines and organizations, we encourage your application.

The OPASI's primary objective is to develop: a transparent process of planning and priority-setting characterized by a defined scope of review with broad input from the scientific community and the public; valid and reliable information resources and tools, including uniform disease coding and accurate, current and comprehensive information on burden of disease; an institutionalized process of regularly scheduled evaluations based on current best practices; the ability to weigh scientific opportunity against public health urgency; a method of assessing outcomes to enhance accountability; and a system for identifying areas of scientific and health improvement opportunities and supporting regular trans-NIH scientific planning and initiatives.

As the DESA Director, you will be responsible for planning, conducting, supporting, and coordinating, specific program evaluations and projects of NIH Institutes and Centers such as the Roadmap, Obesity, and Neuroscience Blueprint initiatives. In addition, you will serve as the liaison for conducting governmentally required assessments according to the Government Performance and Results Act (GPRA) and OMB Program Assessment Rating Tool (PART). You will also serve as a member of the OPASI Steering Committee involved in oversight of institution-wide planning and analysis.

Salary is commensurate with experience and includes a full benefits package. A detailed vacancy announcement with the mandatory qualifications and application procedures can be obtained on **USAJOBS at www.usajobs.gov (announcement number OD-08-230779-T42) and the NIH Web Site at http://www.jobs.nih.gov**. Questions on the application procedures may be addressed to **Brian Harper on 301-594-5332**. Applications must be received by midnight eastern standard time on **February 18, 2008**.

Division Director, Experimental Hematology and Cancer Biology

The Division of Experimental Hematology and Cancer Biology at Cincinnati Children's Hospital Medical Center is initiating a search for an outstanding scholar and leader. The successful applicant may hold an MD, PhD or combined MD/PhD degrees. S/he may have a translational or basic focus in cancer or hematopoesis, including but not limited to stem cells. Very significant resources are available to build a joint cancer program with the University of Cincinnati. The successful candidate will be expected to maintain and advance outstanding scientific programs, and lead a collaborative, translationally-oriented division with extensive external funding.

The division currently houses 16 faculty members with strength in hematopoesis, neuro-oncology, signaling and gene therapy. The division maintains outstanding cores for vector development, flow cytometry, mouse modeling, and pre-clinical translational laboratories, and is moving to a new research building in January 2008. Cincinnati Children's is currently ranked second in NIH funding for Departments of Pediatrics and in the top five in Pediatric Cancer Care. Ample laboratory space in the new building and a generous multi-year start-up package will be provided.

Applications should be emailed to:
Jeff.Robbins@cchmc.org

Cincinnati Children's® Hospital Medical Center

Visit our website at
www.cincinnatichildrens.org

Cincinnati Children's Hospital Medical Center is an Affirmative Action/Equal Opportunity Institution. Women and minorities are encouraged to apply.

Princeton University seeks nominations and applications for the position of Director of the Princeton Plasma Physics Laboratory, PPPL. Princeton University manages and operates PPPL under contract with the U.S. Department of Energy (DOE) and funding for the Laboratory comes primarily from the Office of Fusion Energy Sciences within the DOE Office of Science. Princeton University will propose to continue to manage and operate PPPL after its current contract expires on September 30, 2008. It is expected that the successful candidate will help prepare Princeton's proposal and will begin to serve as Director as soon as possible. The Director of PPPL is normally appointed to the faculty at Princeton University.

The Director of PPPL oversees an $80M per year scientific program with a staff of 450. The Director is responsible for leading the Laboratory's highly collaborative scientific programs in fusion energy science and technology, as well as broader investigations in plasma science, for providing leadership to the U.S. and world fusion research effort, and for assuring that PPPL in all respects meets DOE's highest standards for safe, efficient and compliant operations. The Director of PPPL reports to and serves as an ex-officio member of the PPPL Management Board, composed of the President, Provost, Dean of the Faculty, and Dean for Research.

Candidates should be outstanding scientists with extensive records of scientific and technical accomplishments and demonstrated success in leading and managing large scientific programs or organizations. This position requires an individual with a proven track record of exemplary, senior-level leadership, and a vision to foster a culture of innovation and collaboration. Prior experience with and understanding of the operations and expectations of the DOE are highly desirable. Ability to communicate effectively with staff, researchers, government officials and press is essential.

Applications should be submitted online to **http://jobs.princeton.edu**. Nominations may be sent to: **Prof. A J Stewart Smith, Dean for Research, Princeton University; dfr@princeton.edu**. To receive full consideration, nominations and applications should be received by **March 15, 2008**.

Princeton University is an Equal Opportunity Employer and complies with applicable EEO and affirmative action regulations. Applications from women, ethnic minorities, veterans and individuals with disabilities are encouraged.

MSSM
MOUNT SINAI SCHOOL OF MEDICINE

www.mssm.edu

POSTDOCTORAL FELLOW POSITIONS

Philadelphia Chromosome Negative Myeloproliferative Disorders

The Department of Medicine at the Mount Sinai School of Medicine is currently seeking two full time Postdoctoral Fellows to work in a vigorous research laboratory to participate in molecular and cell biological studies of myelofibrosis, polycythemia vera as well as essential thrombocythemia. Requires a Ph.D or M.D or an equivalent degree in the biological sciences, with demonstrated expertise in molecular, cellular, and biochemical techniques as well as the ability to work within a research team. A strong background in hematopoietic stem cell biology, molecular genetics and drug development essential (candidates without this background are still encouraged to apply).

Please send a brief statement of research experience and interest, CV, and contact information for three references to: **Ronald Hoffman, M.D, Albert A. and Vera G. List, Professor of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, NY, NY 10029 or email: ronald.hoffman@mssm.edu.** EOE.

Inaugural

National Security Science and Engineering Faculty Fellowship Competition

Nominations open on Jan. 8th, 2008
Nominations deadline is Feb. 21st, 2008

- Basic research grant of $600K/year for up to five years to outstanding faculty whose PhD was awarded within the past 25 years.
- Nominations from accredited, degree-granting Institutions.
- Open to all disciplines. For a list of DoD-relevant technologies, see the website below.
- Two stage evaluation: brief white papers, then full proposals and interviews with finalists.
- Research conducted under this program will be unclassified.
- Security clearance not required at time of application. If selected as a finalist, an application for clearance must be submitted. Secret security clearance required for final award.

Visit nsseff.ida.org for full announcement, rules, and nomination procedures

Department of Defense
Director, Defense Research and Engineering

For further information call Deputy Under Secretary of Defense for Laboratories and Basic Sciences, (703) 588-1372

CNETHPC, the NATIONAL CENTRE FOR HYDROGEN AND FUEL CELL TECHNOLOGY EXPERIMENTATION is looking for a:

DIRECTOR

The NATIONAL CENTRE FOR HYDROGEN AND FUEL CELL TECHNOLOGY EXPERIMENTATION (CNETHPC) is a new Spanish facility for hydrogen and fuel cell research and development, created as a Consortium of the Spanish Ministry of Education and Science and the Castilla-La Mancha Regional Government, as a part of the implementation of the Spanish Roadmap of Scientific and Technological Facilities.

The CNETHPC is devoted to scientific research and technology development in all the fields related to hydrogen and fuel cell technologies, being at the service of the national research and technology community and open to international access and collaboration.

The Director reports to the Governing Council and is responsible for the management of the construction and operation, and for maximizing its readiness and effectiveness for scientific research. The Director takes care of the recruiting and maintenance of high quality scientific, technical and administrative staff, developing an annual budget for review and approval, and proposing the short-and-long-range plans for the Centre.

Salary range and start date are to be negotiated.

Review of applications will begin on February 2008, and the recruitment will continue until the position is filled with a proper candidate.

Additional information on the duties or any other aspect concerning the position can be found at **http://www.cnethpc.es.** For any question or request, please send an e-mail to **sgpitgi@mec.es and cneh2pc@jccm.es.**

UNIVERSITY OF KONSTANZ

KoRS-CB, will commence its training program in April 2008. Thus, KoRS-CB invites applications for

Fellowships for Ph.D. students

from highly motivated and enthusiastic students with a keen interest in interdisciplinary research and an excellent degree (Master or Diploma) in Biology, Chemistry or related areas.

For details on the application procedure and further information on the research and training program of KoRS-CB, the participating Departments, and the University of Konstanz, please visit the KoRS-CB homepage at
www.chembiol.uni-konstanz.de

HOSPITAL FOR SPECIAL SURGERY

CORNELL UNIVERSITY
Joan and Sanford I. Weill Medical College

FACULTY POSITIONS
Bone Biology
Musculoskeletal Pathophysiology

The Research Division of the Hospital for Special Surgery, in conjunction with the Weill Cornell Medical College, is developing research programs in bone biology. We seek candidates with interests and demonstrated expertise in bone cell and molecular biology, osteoblast function and bone formation, and in vivo models of musculoskeletal disorders for tenure track faculty positions. Candidates with experience in systems biology, biophysics and osteoimmunology will also be considered. Evidence of continuous NIH or other extramural funding is desirable, and a record of continuing research productivity is required.

The Hospital for Special Surgery Research Division maintains an independent research program with faculty affiliated with Weill Cornell Medical College and the Bioengineering Programs at the Cornell University Sibley School of Engineering and at the City College of New York. Faculty is expected to develop an independent extramurally funded research program and to participate in the academic programs of Cornell University, where they will hold joint appointments. There will be ample opportunity for collaboration with clinical investigators and scientists at the adjacent campuses of Weill Cornell Medical College, the Sloan-Kettering Institute and Rockefeller University. Details on HSS research programs and its NIH funded Musculoskeletal Repair and Regeneration Core Center (MRRCC) can be found at **http://www.hss.edu/research.asp**.

HSS offers an extensive startup package and a highly competitive compensation package. Applicants should send a CV along with a statement on research interests and a list of references by mail to: **Dr. Lionel Ivashkiv, Chair, Research Search Committee, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021** or by email to **mrakv@hss.edu**.

The Hospital for Special Surgery is an Equal Opportunity, Affirmative Action Employer; women and minorities are strongly encouraged to apply.

If you are looking to recruit top-level scientists for your research and faculty positions or brand your organisation, turn to *Science*. Run your ad alongside this article— your listing will get the attention and applications you want, and the results you need.

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FACULTY POSITIONS

WRIGHT STATE UNIVERSITY

Assistant Professors
Tenure Track
Department of Biochemistry and Molecular Biology
Wright State University
Boonshoft School of Medicine and College of Science and Mathematics

The Department of Biochemistry and Molecular Biology invites applications from outstanding candidates for two faculty positions at the assistant professor level. This is the first wave of a faculty expansion following the department's recent move into the Matthew O. Diggs III Laboratory for Life Sciences. These are tenure-track, nine-month appointments with competitive startup packages and the opportunity to occupy state of the art research space. Applicants must have a Ph.D., M.D., or equivalent doctoral degree, two or more years of postdoctoral experience and research interests that align with one of the position descriptions below. Applicants are expected to establish funded, independent research programs and participate in collaborative projects with current faculty. Candidates with research interests that build on existing departmental strengths are particularly encouraged to apply.

The department currently consists of 10 full-time faculty actively engaged in research in the areas of molecular genetics and biochemistry. Specific descriptions of the research interests desired for each position are:

Position 08Y-MG: Assistant Professor in Molecular Genetics: The research interests of the successful applicant will intersect with those of present faculty studying the regulation of gene expression (Kadakia, Paietta, Paliy), oncogenesis (Berberich), genomics (Markey), or DNA replication and genome instability (Leffak, Liu).

Position 08Y-BCH: Assistant Professor in Biochemistry: The research interests of the successful candidate will intersect with those of current faculty involving molecular bioenergetics (Prochaska, Fleischman), metabolomics (Reo), or the molecular basis of protein function (Alter).

Please send a letter of application, curriculum vitae, a focused research plan, and the names and contact information for three references to: **Dr. Steven Berberich, Chair, Department of Biochemistry and Molecular Biology, Wright State University, 3640 Colonel Glenn Hwy, Dayton, OH 45435**. Indicate in your cover letter the position for which you wish to be considered. Review of applications will begin on **March 10, 2008** and continue until the positions are filled. Please visit **http://www.med.wright.edu/bmb/** to learn more about the department, the university and the Dayton area.

Wright State University is an Equal Opportunity/ Affirmative Action Employer.
Candidates from groups underrepresented in academic science are strongly encouraged to apply.

POSITIONS OPEN

Where Cures Begin

The Salk Institute for Biological Studies, a world class scientific environment and workplace located in La Jolla, CA, has exciting opportunities available for the following:

Postdoctoral Positions

There are two positions available: The first position is to study how stem cells differentiate into neurons by developing new technologies to investigate the process on the molecular level. This project is supported by the California Institute for Regenerative Medicine. The second position is to study the molecular mechanism of synaptic vesicle exocytosis using genetically encoded unnatural amino acids. Both positions will be available for 12 months with the possible extension of up to 4 years.

Candidates should have a recent Ph.D. (within two years) and a strong background in cell biology or molecular biology. Training in molecular neurobiology and experience with stem cells are highly desirable.

Please send CV, a brief statement of research experience, and names of three references to: **Lei Wang, Ph.D., Chemical Biology and Proteomics Laboratory, The Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037.**
E-mail: lwang@salk.edu.
http://www.salk.edu/faculty/faculty_details.php?id=67. EOE.

SALK INSTITUTE FOR BIOLOGICAL STUDIES

FACULTY POSITIONS

Tufts UNIVERSITY | Cummings School of Veterinary Medicine

Assistant/Associate/Full Professor in Microbiology/ Infectious Diseases

Tufts Cummings School of Veterinary Medicine, with well developed programs in biodefense/emerging infectious diseases, is seeking applications from outstanding candidates for two faculty appointments at the assistant to full professor levels. Individuals will strengthen and complement existing programs in the Division of Infectious Diseases. Appointees will occupy the state-of-the-art New England Regional Biocontainment Laboratory (RBL) one of thirteen funded by the NIAID. The RBL, slated to open early 2009, will have office and BSL3 space, as well as BSL3 vivarium inclusive of aerobiology and insectary units. Candidates with continuous successful history of NIH funding are sought, and will be expected to form the future scientific and administrative leadership of the Division.

The Division is a dynamic group of approximately 70 including faculty, scientists, laboratory and animal technicians, graduate students and administrative staff. The Division currently occupies two buildings containing modern laboratory facilities and equipment, and has access to diverse animal models, small and large, housed under various biocontainment levels.

Currently funded research programs (by NIH, EPA, DOD, AWARF, Gates Foundation and private sector) include: *E. coli* O157 and associated conditions including HUS; cryptosporidiosis; microsporidiosis; botulinum intoxication therapy; water/food safety and biosecurity; schistosomiasis; tularemia and tick borne diseases; shigellosis; *C. difficile*; and enteric virology. (**www.tufts.edu/vet/biomed/infectious_diseases.htm**)

Please submit a curriculum vitae, letter describing qualifications, highlighting relevant experience, administrative philosophy, and full contact information for four references to: **Saul Tzipori**, Chair, Search Committee, at **saul.tzipori@tufts.edu**. Application review will continue until positions are filled. For questions, e-mail or call **508-839-7955**.

Tufts University is an Affirmative Action, Equal Opportunity Employer.

DIRECTOR
HUMAN NUTRITION RESEARCH PROGRAM

Applications are invited for Director of North Carolina Central University's newly created research programs located in the UNC Human Nutrition Institute on the North Carolina Research Campus (NCRC) at Kannapolis, NC. To learn more about NCRC, please visit **www.ncresearchcampus.net**. The successful candidate will report to the Director of NCCU's Julius L. Chambers Biomedical/Biotechnology Research Institute (JLC-BBRI). Preference will be given to candidates whose research focuses on transgenic zebrafish modeling to study mechanism-based cancer prevention using dietary or pharmaceutical agents.

Candidates will be expected to: have a strong track-record of extramural funding and research productivity; develop collaborations with NCRC and other investigators studying nutrigenomics; have experience in graduate student training; and provide scientific and administrative leadership for all NCCU research projects/programs in nutrigenomics. Applicants must hold a Ph.D. and/or M.D. and meet requirements for a tenure-track faculty appointment at the Associate Professor or Professor level in an NCCU basic science department.

Review of applicants will begin immediately and will continue until the position is filled. Applicants should submit by mail or email *curriculum vitae*, a description of research interests, and contact information for three references to: **Connie Key, Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, 700 George Street, Durham, NC 27707, Email: chkey@nccu.edu**.

For more information about the BBRI and NCCU visit:
http://www.nccu.edu/BBRI

North Carolina Central University is a constituent institution of the University of North Carolina System and an Equal Opportunity, Affirmative Action Employer. NCCU complies with the Immigration Reform and Control Act of 1986.

Lymphoma Research
Massachusetts General Hospital Cancer Center and Harvard Medical School

The Massachusetts General Hospital Cancer Center is seeking to recruit an investigator with a strong research interest in the biology and/or treatment of lymphomas. We seek outstanding individuals with a strong ongoing research program in this area who will be interested in engaging both with physicians at MGH with an interest in lymphoma, as well as with the large community of scientists and physician/scientists at the MGH Cancer Center. Candidates at any stage of their career are encouraged to apply. Applications from women and minority candidates are strongly encouraged.

Candidates should submit a curriculum vitae including a full list of publications and a brief statement of research interests to the address below. Letters of reference may be sought at a later stage in this process.

Lymphoma Search Committee
c/o Carol Ann Hannan
MGH Cancer Center
13th Street, Building 149, Room 7204
Charlestown, MA 02129

Applications must be received by **March 15, 2008**.

Massachusetts General Hospital and Harvard University uphold a commitment to Affirmative Action and Equal Opportunity.

FACULTY POSITIONS

SAINT LOUIS UNIVERSITY

FACULTY POSITION IN CARDIOVASCULAR BIOCHEMISTRY
DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
SAINT LOUIS UNIVERSITY SCHOOL OF MEDICINE

Saint Louis University, a Catholic Jesuit institution dedicated to student learning, research, health care, and service is seeking applicants for a faculty position in the Edward A. Doisy Department of Biochemistry and Molecular Biology for a tenure-track position involving research and teaching at the ASSISTANT PROFESSOR level, although outstanding candidates at a more senior level will be considered. The department is housed in the E.A. Doisy Research Center, a brand new state-of-the-art facility designed to foster collaboration between investigators. We seek applicants who use innovative approaches in the areas of cardiovascular biology, metabolism and signaling. Cardiovascular research is a growing focus area at the School of Medicine with strengths in lipidomics, cell signaling, systems biology and molecular basis of cardiovascular disease. We are interested in a highly interactive candidate whose interests will complement ongoing research programs in the cardiovascular sciences in the Department as well as the University.

The successful candidate is expected to establish a strong extramurally funded research program. A potential for or demonstrated evidence of competing successfully for external funding will be important criterion for selection. Excellent start-up funds and salary are available. Interested candidates must submit a cover letter, application and current curriculum vitae to **http://jobs.slu.edu**. Additionally send current curriculum vitae, description of research plans, and at least three letters of recommendation to: **Search Committee, c/o William S. Sly, M.D., Chairman, Edward A. Doisy Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine, 1100 South Grand Blvd., St. Louis, MO 63104-1028.**

Saint Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations and applications of women and minorities.

Discover Life + Science

...in the heart of North Carolina's pharmaceutical discovery zone!

SCYNEXIS, Inc. is a dynamic company that delivers safe, effective and innovative drug pipeline solutions. SCYNEXIS' continuous innovation has opened new opportunities and therefore we seek the following highly motivated and technically skilled scientists:

Insect Target Biologist, MS or PhD

Successful candidates will have a degree in biochemistry, molecular biology or equivalent training and a background in insect physiology, neurobiology, and/or toxicology with a proven track record in the development and implementation of *in vitro* target-based, cellular, tissue and model organism assays for compound discovery. Experience with genetic techniques is a plus.

Biochemist, BS or MS

Successful candidates will have a background in cell and molecular biology and a proven track record in the development and implementation of *in vitro* target-based, cellular and tissue assays to identify and validate novel druggable targets. Experience in determining the mode of action of clinical candidate compounds is required. An understanding of HTRF-FP-Alpha Screen assay development, binding assays, and/or bioinformatics is a plus.

Bioanalytical Mass Spectrometrist, PhD

This position performs quantitative and qualitative LC-MSMS method development and subsequent bioanalysis for small molecule or biotech therapeutics in biological fluids or tissues. Method development includes selection and optimization of sample extraction techniques. Successful candidates will have a passion for innovation and achievement and will be given developmental opportunities in pre-clinical pharmacokinetic study design and data analysis.

Analytical Research & Development Leader, PhD

This leader will be responsible for developing and validating analytical methods in support of the development of active pharmaceutical ingredients (APIs). A PhD with 3+ years of experience in an industrial setting is required. Candidates must have experience in HPLC and GC method development to be considered. The ability to manage in a team environment and handle multiple projects is a plus.

Parasitologist, BS, MS or PhD

This person will develop and validate assays, screen compounds in several whole organism and target-based assays, maintain and trouble-shoot assay instrumentation and procure and maintain parasitic organisms. Assimilation and analysis of assay data including data collection, reporting and presentation of results from *in vitro* and *in vivo* bioassays for the purposes of compound progression conducted as part of the discovery of anti-parasitic compounds is also a major function. Additionally, this scientist will plan and execute external work with outside collaborators. Successful candidates will have a degree in parasitology, biology or a related field or relevant experience and a proven track record working with industrial collaborators.

Bioanalytical Scientist, BS

This position uses LC-MSMS to determine small molecule or potential biotech therapeutics present in biological samples. Successful candidates will have a sound understanding and practical experience with applied LC-MSMS for quantitative analysis, ideally in support of *in vitro* and *in vivo* DMPK studies and be experienced in quantitative analysis with a focus on HPLC-based methods, and in performing quantitative LC-MSMS analysis. Working to GLP and Pt11 compliance standards and experience using Applied Biosystems triple quadrupole mass specs is a must. LC-MS/MS method development experience is a plus.

DMPK Research Scientist, PhD

This person designs and leads *in vivo* discovery and pre-clinical DMPK studies in lead optimization and candidate selection activities across therapeutic programs in human and animal health, including developing protocols, preparing dose materials, coordinating in-life activities with external facilities, calculating PK parameters, and interpreting and reporting PK data to project teams. Successful candidates will have a PhD in animal health, animal/human physiology, toxicology or pharmaceutical science.

SCYNEXIS offers a competitive compensation and benefits program, including a 401k with company match, relocation and stock options. Please send cover letter and resume to: **ushuman.resources@scynexis.com** or mail to: SCYNEXIS, Inc., Attn: HR, PO Box 12878, Research Triangle Park, NC 27709.
EOE

SCYNEXIS™

FACULTY POSITIONS

ASSISTANT/ASSOCIATE PROFESSOR
Division of Pharmacology and Toxicology
University of Missouri, Kansas City
School of Pharmacy

The Division of Pharmacology and Toxicology in the School of Pharmacy invites applications for a 12-month, tenured, or tenure-track position at the Assistant/Associate Professor level. Applicants should possess a Ph.D., Pharm.D., or M.D. in pharmacology, neuroscience, toxicology, or a related discipline. Preference will be accorded to applicants with interdisciplinary research experience involving neuroscience, pharmacogenomics, substance abuse, or translational research; outstanding candidates from other relevant areas are also strongly encouraged to apply. The successful applicant at the Associate Professor level is expected to have a vigorous, well-established, and externally funded research program, and to provide instruction in the Doctor of Pharmacy Professional Program and Dental Pharmacology Program. The position includes excellent compensation, startup package, and comprehensive benefits. Application review will begin immediately, and will continue until the position is filled. All final candidates will be required to successfully pass a criminal background check prior to beginning employment. University of Missouri, Kansas City (UMKC) is a comprehensive research university exemplifying the values of education first, innovation, accountability, diversity, and collaboration. More about UMKC is at **website: http://www.umkc.edu,** or go to **website: http://pharmacy.umkc.edu.** Applicants should electronically submit a cover letter and curriculum vitae with research plan, and arrange to have letters from three professional references e-mailed to:

Anil Kumar, Ph.D., Chair, Search Committee
Division of Pharmacology and Toxicology
University of Missouri, Kansas City
Health Sciences Building
2464 Charlotte Street
Kansas City, MO 64108-2718
Telephone: 816-235-2415
E-mail: kumaran@umkc.edu

UMKC is an Affirmative Action/Equal Opportunity Institution.

The MIT Department of Mechanical Engineering invites applications for a **FACULTY POSITION** in the field of robotics, mechatronics, and dynamic systems and control. The successful candidate should have demonstrated abilities to conduct a strong research program as well as to teach graduate and undergraduate subjects in these areas. The field of robotics, mechatronics, and dynamic systems and control has entered a new era with advanced sensors, actuators, materials, and communication technology. Growing needs include autonomous mobile robots for energy exploration, security, defense, and environment monitoring; advanced medical devices and systems for surgery, rehabilitation, and elderly care; and humanoids and home robots for home automation, education, and entertainment. Applicants must hold a Doctorate in a discipline related to one or more of the above research topics.

Applications will be reviewed as soon as they are received. Any applications received by April 1, 2008, will receive full consideration. Applicants should send curriculum vitae, a statement of research and teaching interests, no more than five publications, and contact information for at least three references. E-mail applications are preferred; send to **e-mail: robotics-mesearch07@mit.edu** in M.S. Word, PDF, or plain text. Alternatively, send two copies of these documents to: **Chair, Robotics, Mechatronics, and Control Search Committee, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Room 5-214, Cambridge, MA 02139-4307.**

See **websites: http://web.mit.edu/** and **http://meche.mit.edu/.**

MIT is especially encouraging minorities and women to apply, because of its strong commitment to diversity in engineering education, research, and practice.

MIT is an Affirmative Action/Equal Employment Opportunity Employer.

POSITIONS OPEN

Smithsonian Tropical Research Institute
IS SEARCHING for a RESEARCH SCIENTIST

The Smithsonian Tropical Research Institute (STRI), headquartered in the Republic of Panama, is seeking world-class scientists to establish research programs in any current field of marine or terrestrial research, working anywhere in the tropics. These fields include all biological sciences, anthropology, archaeology, paleontology, geology, and soils science. Ideally, research initiated by the successful applicants will complement existing programs (see **website: http://www.stri.org).** We are especially interested in research on vertebrate biology, anthropology and archaeology, paleontology, and climate change.

Panama and adjacent regions of tropical America are rich in terrestrial and marine habitats, archaeological sites, and geological deposits. STRI maintains sophisticated research laboratories, a library, and support centers, in Panama City, as well as diverse facilities for field research throughout the tropics. A 100-foot vessel is available for marine and coastal research. STRI scientists maintain cooperative research programs with a worldwide network of institutions. Opportunities for mentoring young scientists are available through a vigorous fellowship program, and formal teaching is possible through programs with affiliated universities.

Applicants should have a Ph.D. degree and postdoctoral research experience in their fields. Interested candidates should submit a summary of research accomplishments and interests, curriculum vitae, five significant reprints, and the names and contact information of three potential referees.

Annual salary is commensurate with experience. Laboratory set-up and relocation expenses are provided. Housing and family education allowances may apply. Spanish-English bilingual education is available in some Panamanian schools, which follow international curricula and standards.

Review of applications will begin in April 2008. Please send applications electronically to the: **Director of Smithsonian Tropical Research Insititute, c/o Ms. Luz Latorraca, Office of Human Resources, e-mail: latorral@si.edu.** Address inquiries to: **Dr. William Wcislo, Chair, Search Committee, e-mail: wcislow@si.edu.**

STRI is an Equal Opportunity Employer and appointments are made regardless of nationality.

POSTDOCTORAL POSITION in CANCER RESEARCH

The University of Illinois at Chicago Cancer Center is seeking a highly motivated Postdoctoral Fellow with a Ph.D. in biochemistry, molecular biology, or closely related biological sciences to conduct cancer research. Experience in molecular genetic techniques and cell culture systems desirable, excellent communication skills, and strong record of independent research skills essential. For fullest consideration, send resume, cover letter with a statement of research interests, and names of three references by February 15, 2008, to: **Ms. Dorothy Sholeen-Modrzyk, University of Illinois at Chicago Cancer Center, MC 700, 914 South Wood Street, Chicago, IL 60612,** or **e-mail: cancer@uic.edu.** *UIC is an Affirmative Action/Equal Opportunity Employer.*

POSTDOCTORAL POSITIONS available immediately to study the genetics and cell and molecular biology of aging in yeast (e.g. see *Aging Cell* **6:** 405, 2007). Send curriculum vitae and three references to: **S. Michal Jazwinski, Ph.D., Tulane Center for Aging, Tulane University Health Sciences Center, 1430 Tulane Avenue, SL-12, New Orleans, LA 70112.** Electronic applications **(e-mail: sjazwins@tulane.edu)** will receive prompt attention. *Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITIONS

CHAIR
Department of Medicinal and Biological Chemistry

The Department of Medicinal and Biological Chemistry of the University of Toledo College of Pharmacy invites nominations and applications from a senior investigator with a distinguished record of teaching and research to take on leadership of the Department. The Department currently consists of nine full-time faculty with a long history of competitively funded research. Faculty research includes fundamental problems of therapeutic drug design as well as basic biological and chemical research to reveal novel therapeutic targets. The Department has M.S. and Ph.D. Programs in Medicinal Chemistry with 25 to 30 graduate students. The faculty also takes an active role in the B.S. Program in Pharmaceutical Sciences and in the Pharm.D. Program.

Candidates must have a Ph.D. degree in medicinal chemistry, biochemistry, or related field, and a track record of scholarly activity commensurate with an academic appointment at the rank of professor. The successful candidate will be expected to maintain and augment existing research and training programs and to lead the Department during an era of growth and development. There will be an attractive startup package. For additional information about the Department please visit our **website: http://www.utpharmacy.org/mbc-overview.asp.** Forward nominations or applications with current curriculum vitae, and names and contact information of not less than three references to: **Dr. William Messer, Chair of the Search Committee, The University of Toledo College of Pharmacy, Department of Pharmacology, 2801 West Bancroft Street, Toledo, OH 43606-3390; telephone: 419-530-1910; fax: 419-530-1909; e-mail: mbcchairsearch@utoledo.edu.** Reference position PCN 996685. The review of applications and nominations will begin March 1, 2008, and continue until the position is filled. *The University of Toledo is an Equal Opportunity/Affirmative Action Employer.*

IMMUNOLOGY ASSISTANT PROFESSOR
University of Minnesota

The Department of Laboratory Medicine and Pathology in the University of Minnesota Medical School, in collaboration with the Center for Immunology, is seeking to hire a tenure-track faculty candidate.

Candidates should have experience, interest, and demonstrated productivity in basic aspects of innate or adaptive immunity, using either human or animal models. Candidates must hold a Ph.D., M.D., or equivalent degrees, and have at least three years of relevant postdoctoral experience. The successful candidate will be expected to develop an independent and innovative externally funded research program, and will have the opportunity to participate in the teaching mission of the University. The goal is to broaden the range of expertise and research programs within the Center for Immunology.

Interested candidates can learn more about faculty interests, facilities, and educational programs at websites for the Center **(website: http://www.immunology.umn.edu/),** the Department **(website: http://pathology.umn.edu/),** and the Microbiology, Immunology, and Cancer Biology Graduate Program **(website: http://www.micab.umn.edu/).**

Please submit curriculum vitae, cover letter detailing your fit for the position, and the names and addresses of three (or more if needed) references via the University of Minnesota employment website. Copy and paste the following into your web browser and this will take you directly to the posting: **website: http://employment.umn.edu/applicants/Central?quickFind=68667.** Alternatively you can go to the employment **website: https://employment.umn.edu/applicants/jsp/shared/frameset/Frameset.jsp?time=1198012111653** and search for the requisition number 152691.

POSITIONS OPEN

Columbia University Medical Center, Division of Infectious Diseases is seeking a **POSTDOCTORAL RESEARCH SCIENTIST.** Research involves the pathogenesis/epidemiology of *S. aureus* infections. Studies include analysis of *S. aureus* adhesins and use of animal models to study in vivo gene expression. Experience in molecular biology necessary. Send curriculum vitae to: **Frank Lowy, M.D., 630 West 168th Street, P and S Box 82, New York, NY 10032. E-mail: infectious_diseases@columbia.edu.** *Columbia University is an Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITIONS

SENIOR MELANOMA RESEARCH PROGRAM DIRECTOR

John Wayne Cancer Institute at Saint John's Health Center is a cancer research institute dedicated to the understanding and curing of cancer in order to eliminate patient suffering worldwide. Our mission is accomplished through innovative clinical and laboratory research and the education of the next generation of surgical oncologists and scientists.

Individual needed to oversee the administration of the Melanoma Research Program and to participate in melanoma research.

Position assists the Chief of the Melanoma Program in planning and developing new research programs including facilitating communications on scientific issues and coordinating interactions with research collaborators. In addition, individual will organize the administrative functions of the Program. Requires application of scientific knowledge, tactful guidance, and competent management of operational functions with the goal of establishing worthwhile and well-run scientific programs, and identification of new program opportunities.

Qualifications include a M.D. or Ph.D. with background in research and administration of biomedical cancer research and clinical trials, along with five to ten years of increasing responsibility in the management of clinical and research institute and/or hospital administration.

We offer competitive compensation and benefits package, as well as the opportunity to truly impact the conduct and result of medical research. Send curriculum vitae and references to**: Dr. Myles Cabot, John Wayne Cancer Institute, 2200 Santa Monica Boulevard, Santa Monica, CA 90404.** Or **e-mail: sandra.barnes@stjohns.org.**

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FACULTY POSITIONS
Department of Physiology and Biophysics
Case Western Reserve University
Cleveland, Ohio

With the recent recruitment of a new Chair, the Department of Physiology and Biophysics is undergoing a period of major expansion. We invite outstanding individuals to apply for faculty positions at the level of **ASSISTANT PROFESSOR (TENURE TRACK), ASSOCIATE PROFESSOR, and PROFESSOR.** The Department's major areas of focus are protein biophysics/structural biology and all areas of physiology. We especially encourage applicants who are using interdisciplinary approaches to work on basic and translational aspects of human diseases. Visit our **website: http://Physiology.case.edu.**

Applicants should submit a cover letter and full curriculum vitae. Applicants for Assistant Professor positions should include a brief description of their research plans as well as the contact information for three professional references. Please submit application materials by e-mail to:

Walter F. Boron, M.D., Ph.D.
Chairman
E-mail: physiologybiophysicssearch@case.edu

In employment, as in education, Case Western Reserve University is committed to Equal Opportunity and Diversity. CWRU is a recipient of a National Science Foundation ADVANCE Institutional Transformation Grant to increase the participation of women in Science and Engineering."

POSITIONS OPEN

ASU
ARIZONA STATE UNIVERSITY

POSTDOCTORAL RESEARCH ASSOCIATE POSITION in the economics and ecology of ecosystem services in the ecoSERVICES group of the School of Life Sciences, **website: http://www.ecoservices.asu.edu.** Candidates must have earned a Ph.D. in economics, ecology, or a related field at the time of appointment. Experience of interdisciplinary research in these areas is desirable. The post is for two years renewable by mutual agreement. To apply, send curriculum vitae, three research papers, and a statement of research plans, plus names and contact information for three references to **e-mail: charles.perrings@asu.edu.** The initial deadline for receipt of applications is 1 March 2008, with applications reviewed weekly thereafter until the search is closed. *Arizona State University is an Affirmative Action, Equal Opportunity Employer committed to excellence through diversity.*

JUNIOR POSTDOCTORAL RESEARCH SCIENTIST

John Wayne Cancer Institute at Saint John's Health Center is a cancer research institute dedicated to the understanding and curing of cancer in order to eliminate patient suffering worldwide. Our mission is accomplished through innovative clinical and laboratory research and the education of the next generation of surgical oncologists and scientists.

Postdoctoral position available immediately to join a project investigating the influence of ceramide and glycolipids on multidrug resistance associated with the ATP-binding cassette transporter proteins such as P-glycoprotein. Models include breast, ovarian, prostate, melanoma, and gastrointestinal cancers. Recent Ph.D. or M.D./Ph.D. in biochemistry, molecular biology, or cell biology; experience in lipid biochemistry and molecular biology highly desirable.

Send curriculum vitae and references to: **Dr. Myles Cabot, John Wayne Cancer Institute, 2200 Santa Monica Boulevard, Santa Monica, CA 90404.**

Or **e-mail: sandra.barnes@stjohns.org.**

SJHC is an Equal Opportunity Employer.

POSTDOCTORAL FELLOW POSITION

A Postdoctoral position is available immediately in the Institute of Biotechnology/Department of Molecular Medicine at the University of Texas Health Science Center at San Antonio. Our collaborative research project studies estrogen receptor and coregulator function using breast cancer single cell, high content assays. Successful candidates should hold a Ph.D. degree in life sciences, with a record of creativity and scientific productivity. Working experience in molecular and/or cell biology is required. Please provide curriculum vitae, a brief summary of research experience, and the names and contact information of three references to **Zelton Dave Sharp, e-mail: sharp@uthscsa.edu.**

The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer. All Postdoctoral appointments are designated as security-sensitive positions.

POSTDOCTORAL FELLOW

The Department of Biochemistry and Molecular Biology at the University of Kansas Medical Center is seeking a qualified candidate to aid researchers in an active biomedical laboratory. Work will be performed in **Dr. Glen Andrews'** Laboratory. Requires Ph.D. degree in biochemistry, chemistry, molecular biology, or microbiology. To view position description and apply online only go to **website: http://jobs.kumc.edu** and search for position J0010434. *An Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

POSTDOCTORAL/RESEARCH ASSOCIATE POSITIONS are available to study the molecular nature, regulation, and functions of cell calcium and ion channels in cardiovascular, respiratory, and other systems. Research training in general molecular, cancer, stem cell or protein biology, electrophysiology, or calcium imaging is desirable. Salary will be commensurate with experience. If interested, please e-mail application letter and curriculum vitae to **Dr. Yong-Xiao Wang** at **e-mail: wangy@mail.amc.edu. Center for Cardiovascular Sciences, Albany Medical College, Albany, NY 12208.**

AMC supports a diversified, smoke-free environment and is proud to be an Equal Opportunity/Affirmative Action Employer, encouraging women and minorities to apply. In support of a safe, drug-free environment, criminal background checks and drug testing are part of our hiring process.

TISSUE ENGINEER. PROJECT MANAGER for tissue health and seating available at Advanced Platform Technology Center/Cleveland VA. Responsible for all aspects of a research project from grant submission to technology transfer. Make scientific contributions and presentations nationally and internationally Review proposals and journal papers. Requirements: *U.S. citizenship,* Ph.D. in biomedical engineering or closely related field, nine years of research experience in functional electrical stimulation with implantable electrodes and tissue health, and 15 years of experience in field of seating assessment. For specific details regarding position, incumbent requirements and how to apply, refer to **website: http://www.aptcenter.research.va.gov.**

MEDICAL RESEARCHER sought to study the genetic basis of microcephaly. Requirements include M.D. with significant experience in pediatric neurology including ability to perform clinical analysis of research subjects, gene mapping, and cloning. Salary $80,000 per year. Send resumes to: **Christina Venckus, Human Resources, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215.** *BIDMC is an Equal Opportunity/Affirmative Action Employer.*

MARKETPLACE

POSITIONS OPEN

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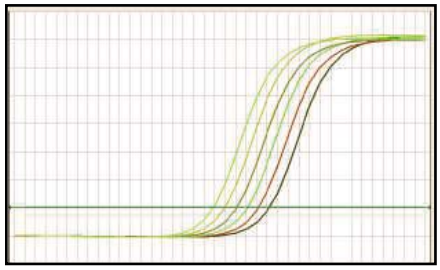

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